Effects on Tissues and Organs (including hereditary and prenatal effects)

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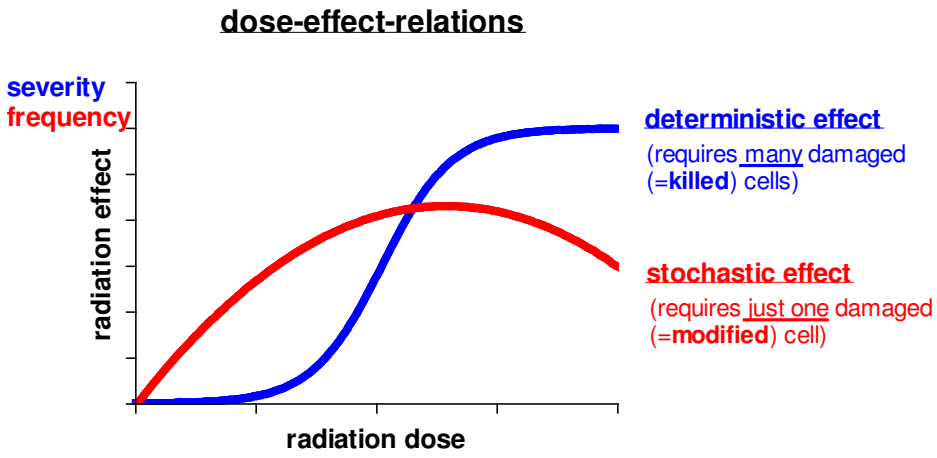
Abstract. A long-standing distinction has been made between "stochastic" and "deterministic" radiation effects. The terms "stochastic" ("random") and "deterministic" ("inevitable") were coined mainly because of epidemiological results and are sometimes mis-leading. There have been suggestions to replace these terms by other ones (e.g. "haplocytic" instead of "stochastic" and "polycytic" or "tissue effects" instead of "deterministic"), but, so far, none of these alternatives succeeded in being broadly accepted. In radiation protection the distinction is important, because in the case of deterministic effects, we are sure that threshold doses exist that must be exceeded, before an effect can be detected, whereas in the case of stochastic effects (tumours and hereditary effects), it is assumed that either no threshold is present at all, or that it is in a very low dose range. Recently, some "established" results have been questioned. This is particularly true for cataracts and cardiovascular diseases. In both cases, it seems to be very probable that the previously assumed threshold doses are too high. If it turns out that this is indeed the case, quite some re-thinking will be required in radiation protection.

KEYWORDS: stochastic, deterministic, hereditary effects, prenatal effects

1. Introduction

One of the most crucial questions in radiation protection is that one referring to the presence or absence of a threshold dose (Fig.1).

Figure 1: Dose-effect-relationships of deterministic and stochastic effects



Stochastic ("random") effects are characterized by the necessity that just one cell is affected (not killed!) by radiation exposure. In the case of hereditary effects, it is obvious that damage to one cell (either oocyte or sperm) is sufficient to cause a hereditary disease. It is not equally obvious in the

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context of tumour induction. On the one hand, it is true that there are strong indications that most tumours originate from one cell, but it is not clear whether this applies to all tumours. On the other hand, carcinogenesis is a multi-step procedure, so that just one hit is not sufficient to produce a clinically manifest tumour. Thus, there might be a threshold in the low dose range ("low dose" means, well below 100 mSv in adults and below 10 mSv in the fetus), but such a threshold has not been shown convincingly up to now. The dependence of the frequency of affected individuals (and not the severity of effect) on radiation dose is another characteristic of stochastic effects.

The situation is somewhat less complicated with respect to deterministic ("inevitable") effects. Deterministic effects derive from the killing or modifying the functional characteristics of **many** cells in a tissue. Many cells cannot be affected by a single energy deposition. This is true even if one takes into account the bystander effect, because in that case more than one cell is affected by one energy deposition, but this "extended" effect is restricted to very few neighbouring cells. Not only fetal tissues are flexible enough to replace a couple of killed cells by healthy ones, but this is also possible in most tissues of the adult, although less efficiently. Cell death is a very common process in the human body: every second more than 3 million cells are dying in our bodies. In the case of deterministic effects, the severity of effect depends on radiation dose. This is simply due to the fact that the number of damaged (killed or functionally modified) cells decides on the degree of effect.

Thus, dose thresholds are to be expected and have been observed in many tissues and organs (e.g. in the lung, the skin, and epithelia in general). On the other hand, one never should be too convinced of results obtained in the past, because from time to time new insights emerge and need a thorough re-thinking of previous concepts. Two examples for such new insights (cataract and cardiovascular diseases) will be addressed in the following among some other aspects.

2. Health effects on tissues and organs

Tissues and organs are a lot more than just the assembly of many cells. There is a high order of organisation with many specialized functions and mutual interactions either directly or via the blood and lymph stream and via the nervous system. Thus, simple cell cultures do not reflect the complex situation of tissues, organs or whole organisms. Quite frequently very surprising effects can be detected in these higher order systems not anticipated from cell culture experiments.

2.1 The cataract issue

All textbooks will claim that cataracts can be induced by ionising radiation, but only after radiation doses exceeding about 2 Gy in the case of an acute exposure and about 5 Gy in the case of chronic exposure. Thus, cataract is looked at as a classical deterministic effect. This assumption has been challenged heavily since a few years. There are new data that, at least, indicate that if threshold doses exist at all, they are markedly lower than assumed previously, and some scientists even doubt that cataract formation actually is a deterministic effect. On the other hand, it does not seem to be a stochastic effect either. It looks as if our useful thinking in just the two categories stochastic and deterministic may not cover the whole field. And this is also an additional reason to use the term "tissue effects" instead of "deterministic effects".

New data were obtained in Hiroshima and Nagasaki [1-3], for astronauts and pilots [4-6], for CT patients [7] and in the vicinity of Chernobyl [8]. In particular, the data of Hiroshima and Nagasaki (acute exposure) and of people in the vicinity of Chernobyl (chronic exposure) indicate that the threshold dose is in the range of 0.1 to 0.8 Gy (Hiroshima and Nagasaki) and around 0.7 Gy (Chernobyl), and it is not unlikely that it is even lower, perhaps even without a threshold at all [1].

One aspect that is important in this context is the necessity to take into consideration that the lower total doses and the lower dose rates are, the longer the latency period is, before effects in the eye can be observed.

2.2 The problem of cardiovascular diseases

Similar to cataracts, it was a long-standing claim that ionising radiation causes cardiovascular diseases only after very high doses as they may occur in radiation therapy with the heart being in the radiation field. Treatment of Morbus Hodgkin was a classical example [9]. Again, the most recent data of Hiroshima and Nagasaki indicate that down to doses as low as 0.5 Gy cardiovascular problems can be detected [10]. Interesting results are expected from the studies of the Mayak workers; these results will be published in the near future.

A major problem with all studies looking at cardiovascular diseases is the high spontaneous number of these diseases and the high number of identified or assumed factors that can cause heart and vascular problems. Thus, there are a lot of confounders which have to be taken care of in epidemiological studies. In addition, we only have very crude ideas on the mechanisms underlying these diseases. A lot of research will be required in the future to clarify the picture.

2.3 The specific problem of abscopal effects

When one is talking about radiation effects on tissues and organs, one should not overlook the possibility of so-called “abscopal effects”, that is, irradiation takes place at a specific location of the human body and radiation effects are observed at a very different location of the body. The mechanism(s) underlying this phenomenon is/are unclear. A role of the immune system is suspected, but has not yet been substantiated.

2.4 Induced clastogenic plasma factors

There are quite a number of reports indicating that after radiation exposure of humans factors are produced in the blood that can provoke chromosomal aberrations in non-irradiated cells. This effect is reminiscent of the bystander effect after irradiating cells in a petri dish, transferring the medium to non-irradiated cells and observing radiation effects in these cells.

It is not known which factor(s) is/are responsible for this observation. There are strong indications that free radicals might be involved, but it is hard to see how they can persist for rather long time intervals. In survivors of the A-bomb attack in Hiroshima and Nagasaki clastogenic factors have been demonstrated decades after the exposure [11]. Possibly, free radicals are produced continuously in these individuals.

2.5 Effects on the immune system

A lot of uncertainties exist with respect to radiation effects on the immune system. This is not surprising taking into consideration the complexity of this system. On the other hand, because of the importance of the immune response deeper insight is urgently required.

In particular, in the low dose range, we, at best, have some qualitative information. But this does not help very much, because in some experiments a stimulation of certain immunologic parameters is observed, whereas other experiments suggest an inhibition. In addition, quite frequently it is completely unclear what a stimulation or an inhibition means with respect to the resulting final radiation risk. A lot of speculation has been expressed in the past, but speculations are only reasonable, when they are followed by studies substantiating or refuting these speculations.

3. Hereditary effects

Until today, there is no convincing evidence for humans that radiation exposure to either mother or father can cause hereditary effects in their offspring. The most thoroughly conducted study in Hiroshima and Nagasaki shows a trend in the expected direction, but this trend is statistically not significant [12,13]. On the other hand, animal studies do show the possibility of the induction of hereditary effects by ionising radiation [14,15]. It is hard to see, why humans should be exceptional. What can be stated, however, is that if a hereditary risk also exists for humans, it will be rather low. This is reflected in the continuous reduction of the tissue weighting factor for the gonads suggested by ICRP, starting 1977 at 0.25, being decreased 1990 to 0.20 and ending up now at 0.08.

4. Effects attributable to prenatal exposure (with emphasis on teratogenesis and mental retardation)

Prenatal radiation exposure still is an issue, in particular, in medicine, because it is not that rare that an exposure occurs due to the ignorance of an existing pregnancy in the course of radiation diagnostics. A pertinent question is whether threshold doses can be expected or not. The answer very much depends on the type of damage that is looked at.

Human pregnancy is sub-divided into three major stages: preimplantation period (weeks 1 to 2), organogenesis (weeks 3 to 7), and fetogenesis (weeks 8 to 39). Radiation effects strongly depend on the stage of pregnancy affected. For all stages, one has to expect induction of childhood cancers, in particular, childhood leukaemias [16,17]. The risk of childhood leukaemias can be shown to be increased down to doses of 10 mGy [18,19]. The doubling dose is in the range of 30 mGy. One must keep in mind, however, that the spontaneous risk is small: about 5 per 100.000 children per year. Thus, a very small risk is doubled by about 30 mGy.

The major effect after radiation exposure of preimplantation stages is embryonic death. The sensitivity varies considerably, sometimes within hours. In the most sensitive phases (shortly after fertilization), effects can be observed down to 100 mGy [20]. It cannot be entirely ruled out that the one or the other malformation is induced also during preimplantation period, but compared to killing of the embryo this will be a rare event [21].

Organogenesis is the period most sensitive with respect to malformations. This has been known for almost 100 years, starting in the twenties of the last century, when physicians used several Gray of ionising radiation in order to induce abortions. Quite a number of the exposed fetuses survived and were born with serious malformations [22]. Threshold doses are to be expected, because it clearly is not sufficient to kill one or a few cells of the developing organ. In addition, fetal tissues are very flexible so that cells that are already on their way to a different function can re-adjust to the function of a killed cell. ICRP came to the conclusion that the threshold dose is in the range of 100 mGy for humans [23]. Some animal experiments point to slightly lower thresholds.

In Hiroshima and Nagasaki no increase of malformations after exposure of organogenesis has been observed. There was, however, a marked increase in mental retardation after exposure during early fetogenesis, most pronounced during weeks 8 to 15 and to a somewhat lower degree during weeks 16 to 25 [24]. There was a long-standing debate on whether a threshold dose exists for the weeks 8 to 15, whereas it was comparatively clear from the beginning that a threshold dose is present for weeks 16 to 25. Biology always pointed to threshold doses for both time periods, because many cells have to be killed or impaired in their migration behaviour in order to cause a severe mental retardation. ICRP meanwhile suggests a threshold dose of about 300 mGy for both time intervals [23]. It is not clear whether a threshold dose exists for IQ reduction. This question will be hard to answer in any case, because even if one assumes a linear dose dependence without a threshold, the risk in the low dose range will be so low that it is impossible to detect it. ICRP estimates the risk to be a reduction of 21 IQ-points per Gray for the weeks 8 to 15, and 13 IQ-points per Gray for weeks 16 to 25. Both numbers do not include the cases of severe mental retardation.

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