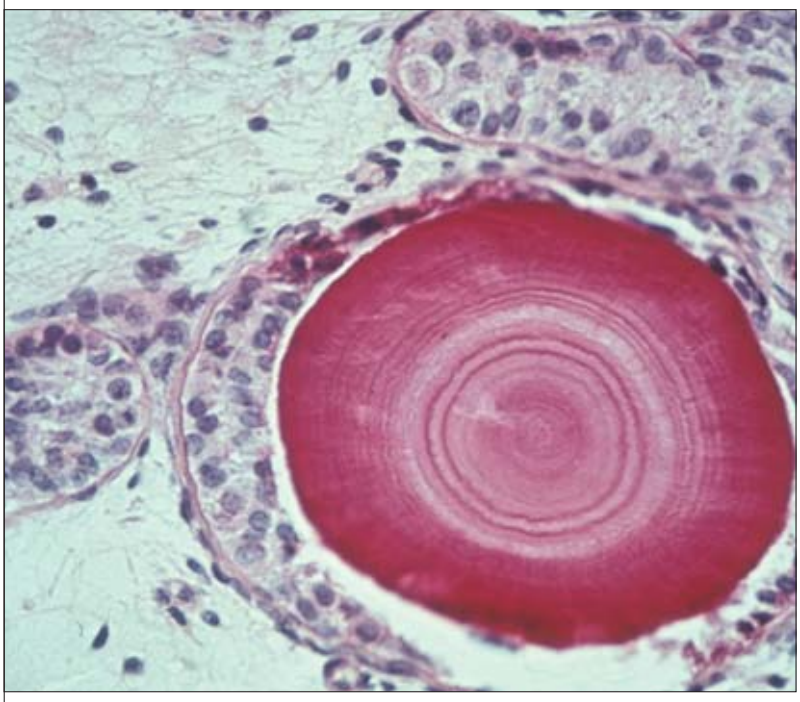
Some hundred years since radioactivity has been first used, although impaired fertility has been observed in persons irradiated at high doses (above 1 Gray in men and at higher doses in women), no human hereditary effects due to ionising radiation have ever been demonstrated, even in populations in whom excess radio-induced cancers have been found, for instance at Hiroshima and Nagasaki. However, the number of successive generations studied may still be insufficient to discern such effects.

The effects of radiation on **reproductive functions**

Radionuclides and gonads: the example of plutonium

Damage caused by the irradiation of the reproductive organs (the gonads, containing germ cells) can produce two types of effect: cell death, with a temporary or permanent reduction of fertility, or mutations in germ cells that can be transmitted after fertilisation and appear as a hereditary disorder in the progeny of the exposed person.



Inserm U293

Human testicle gonadoblastoma. The consequences of high-level irradiation of the gonads strongly depend on when it occurred.

Most of the current data concerning the **exposure** of the gonads (testicles and ovaries) comes from experimental models with **external irradiation**, and concern essentially the consequences on the male gonadic and **germinal** functions. The gravity of damage to the *testicles* depends on the irradiation **dose** and the developmental stage, from fœtus to senescence.
The development of experimental models of gonad irradiation, after **internal contamination**, has been limited: the first experiments carried out with **actinides**, in particular plutonium (Pu), showed no strong affinity for these organs, especially in comparison with the main organs of deposition and retention (such as lungs,bones and liver). The existing data, often old, are summarised hereafter:
The average *fraction retained* in the gonads is estimated in men at 10^{-4}, after an intravenous injection of a soluble form of plutonium. The value for women is ten times lower. The same orders of magnitude were found with other actinides (americium-241, curium-242 and -244 and californium-249). Given the low digestive **transfer factor** for Pu and the other actinides ($\sim 5 \cdot 10^{-4}$), an environmental exposure to Pu should produce a very low concentration in the gonads.
The *retention time* (half life) of plutonium in the testicles, linked to its deposition in the interstitial **macrophages**, is considered as infinite in many species including man. As the retention time in the gonads in certain primates is only about one year, the hypothesis of an infinite retention in man could result in an overestimation of concentration and dose.
The *tissue distribution* is different depending on the sex. In the testicles, plutonium is not distributed uniformly; it is essentially localised in the lysosomal(1) space of the interstitial macrophages, i.e., outside the seminiferous tubules (rat, mouse, dog). In rodents, this mode of retention causes a preferential irradiation of the peripheral spermatogonial germ cells, resulting in a higher dose for these cells than the average dose for the organ. Thus in mice, it is estimated that the dose

(1) Lysosome: membrane organelle of eukaryote cells containing digestive **enzymes**.

for the sensitive cells (spermatogonia) is 2.5 to 4 times higher than the average organ dose.
In the *ovaries* however, there is no preferential localisation of plutonium near the sensitive cells (maturing ovocytes), and the corresponding dose to ovocytes may even be lower than the average dose to the ovary.
In the testicle, it is considered that the cells close to the lumen of the seminiferous tubule are protected from toxic, chemical and **radioactive** aggression by the blood-testicle barrier (BTB). However, recent research in rodents suggests that certain **radionuclides** such as plutonium, americium and polonium could cross the BTB with the physiological iron-**transferrin** pathway. These elements may then bind to meiotic and post-meiotic **germ** cells. This may allow for the direct irradiation of post-spermatogonial cells. As the cells may survive, **mutations** in cells that are already engaged in **differentiation** could be transmitted to the corresponding spermatozoa. As transferrin receptors are expressed by the germ cells of the seminiferous epithelium, an analogous mechanism could be expected in humans.

Targeted studies are now possible

Although the risk of radio-induced hereditary effects does not rank high among the human hazards of **radiation**, and although low levels of contamination by actinides, e.g., Pu, make observable effects on fertility unlikely, some issues specific to problems of contamination remain to be addressed. In the gonads, damage can lead to increased **mutagenesis**, and impairment of **hormone** functions or fertility. Unlike external irradiation, considered as homogeneous in these organs, contamination results in a variable tissue and intracellular distribution that depends on the chemical properties of the contaminant. The consequences in terms of cell damage, both radiological and chemical, are therefore likely to vary according to the chemical nature of the **isotope**, the nature and energy of its emitted radiation, and its **effective half life**. The development in recent years of methods and instrumentation in metrology and molecular biology, genetics and post-genomics, now allows for the development of targeted studies to determine directly the localisation of radionuclides in gonadic and interstitial tissue, as well as the associated biological mechanisms and their consequences.

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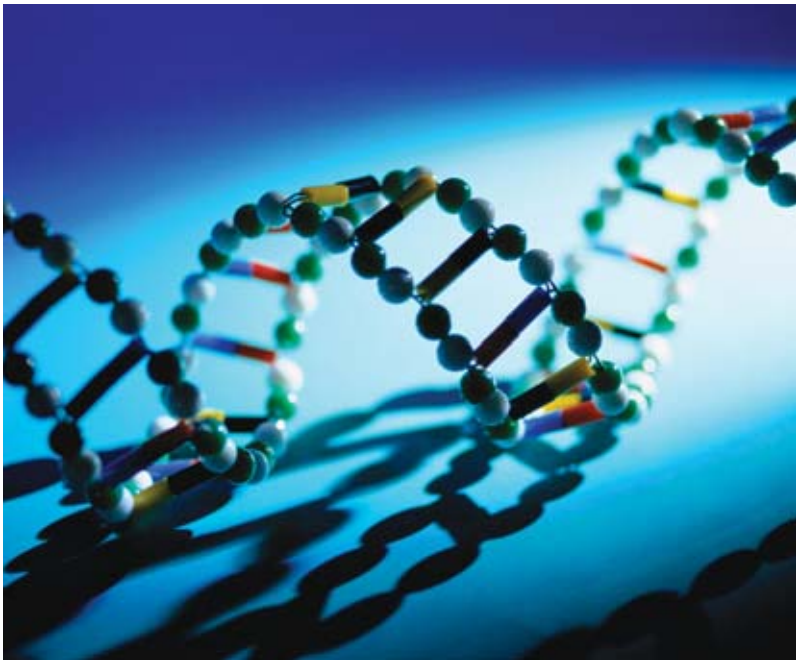
Effects of radiation on genetic material

Knowledge of the effects of ionising radiation on reproductive functions makes it possible to evaluate the early effects of high exposure and to rule out hereditary consequences when transmission to progeny is of the dominant (systematic) type. Conversely, the recessive (conditional) type of transmission can have genetic implications that even if minimal still justify further research.



Lawrence Lawry/PhotoDisc

Model of the DNA molecule, the cell's genetic material, damage to which is the most serious effect of ionising radiation.

There is a long-standing principle that damage to **DNA** is the main adverse effect of **ionising radiation**. The pathogenic character of the DNA lesions is fully expressed only if they affect cycling cells, i.e., proliferative tissue. Other cells, even if damaged, if they are engaged in **differentiation**, can survive with no apparent damage. Their **genetic** material contains sufficient built-in redundancy to operate. The pathogenic potential of damage induced by cycling cells results largely from the control systems in place: these are efficient but not infallible, and can overlook or even generate errors.
The first consequence of induced cell damage can be programmed cell death or **apoptosis**. This is a lesser evil because the damage is eliminated along with the cell. This mortality depends on the **dose** received, and only reaches high levels that threaten the survival of the organ or the individual at high doses of radiation. However, it also depends on the tissue and the time of life of the individual. For the gonads, the sterilisation threshold can vary by a factor of 10 (between 1 and 10 **grays**) according to age and sex.
DNA repair mechanisms must come into play in proliferative cells so they are not blocked in their cycle. This is the case in particular for double

type of lesion	natural without irradiation in 24 h of life	added by 1 Gy of low LET[5] radiation	ratio 1 Gy / natural
single strand breaks	20,000 à 40,000	1,000	1/30
double strand breaks	very few	40	very high
base lesions	20,000	2,000	1/10
other lesions	5,000	200	1/25
total	≃50,000	3,240	1/20

Table. Comparison of the number of radio-induced lesions by type with and without irradiation (1 gray).

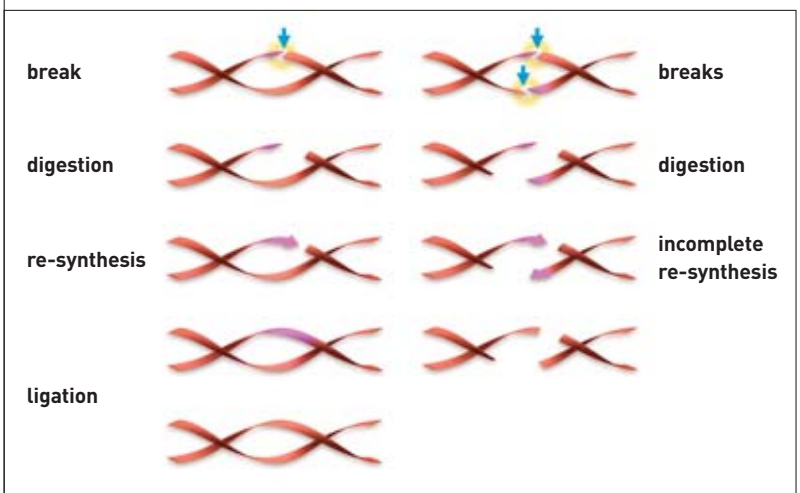
strand breaks[1]: the unit of the affected DNA molecule must be repaired by re-linking the broken ends. However, these repairs can be faulty. The deletion[2] of a few **nucleotides** is the frequent consequence of faulty repair of double strand breaks. This causes a **mutation**, which can be neutral if it affects a non-coding **sequence**. It will then merely result in DNA polymorphism. If it is located in a transcribed sequence (coding a **messenger RNA**), it can cause the loss of a function of the affected **allele**. If the **transcriptional** activity of the other allele suffices to ensure normal function, a *recessive* mutation[3] will be generated. The accumulation of such lesions probably plays an essential role in cancer induction, in particular radio-induced cancers. If the activity of the other allele is insufficient, a *dominant* mutation will be generated. It will persist unless its consequences cause a strong counter-selection of the affected cell.

Another consequence of the **exposure** of the cell to radiation is the installation of **genome** instability, which accelerates the accumulation of mutations that add to those initially induced. These cells thus undergo accelerated senescence[4] with a risk of an escalation towards neoplastic modification, but this process does not seem to generate a significant hereditary risk, although genomic instabilities have been described in the descendants of irradiated persons.

The nature of radio-induced DNA damage

Because of their diversity and their different repair dynamics, it is not easy to draw up a precise schedule of these ***in vivo*** lesions. Those that persist are by definition badly repaired or unrepaired in the surviving cells. However, estimates have been proposed, of which those of Goodhead are the most widely accepted (Table). They compare the effect of an exposure at 1 **gray** (Gy) of radiation with low linear energy transfer[5] with the damage incurred during 24 h of normal cell activity. Overall, such radiation would cause only 6% more lesions. However, the qualitative aspect is more important. It is obvious that a characteristic of radiation is that it causes double strand breaks, which rarely occur naturally. However, even though few in number, these lesions are often badly repaired compared with the others, which are mostly repaired correctly (Figure). As described above, these double strand breaks thus leave a trace, generally a mutation by deletion of some 2 to 30 nucleotides. In addition, several double strand breaks in the same cell can bring about **chromosomal** rearrangements such as long deletions, inversions and translocations if broken ends are linked up wrongly. These rearrangements, if they are balanced, are not detrimental to somatic cells unless they lead to the formation of a chimeric gene with an oncogenic[6] activity, which fortunately seems to be very rare. In the **germinal** line, however, the situation is quite different, because a balanced chromosomal rearrangement can cause mis-segregation during meiosis[7]. Deletions may cause loss of function in a number of genes proportional to their size. Although they are generally well repaired, single strand breaks can still have adverse consequences. **Base** damage is frequent and liable to generate point mutations in rare cases of faulty repair. Two types of mutation are recognised, which differ in their consequences: *non-sense mutations*, able to stop the transcription and which lead to the absence of a **protein**, or to truncated functionless proteins (these mutations are mainly the result of deletions, and their effect at the cell level is often recessive), and *mis-sense mutations*, more often the consequence of base damage, which do not stop transcription, but can change the protein formed. This neo-protein can either acquire a new function, probably a rare occurrence, or lose its function, but still compete with the normal protein. The effect will thus be dominant at the cell scale. These theoretical predictions have been largely confirmed in somatic cells, especially cancerous ones. Data for germinal cells remain very limited.

Figure. Formation of DNA double strand breaks. This occurs when the two breaks are less than 30 base pairs apart.



Particularities of the germinal line

In all tissues, the formation of the germinal line first involves a phase of cell proliferation. This begins during the life of the embryo in both sexes. It does

(1) Double strand breaks: breaks in which both strands of the DNA double helix are severed.

(2) Deletion: loss of genetic material, from a nucleotide to a chromosome fragment.

(3) Recessive mutation: a mutation that affects the organism only if the gene involved occurs on both the chromosomes of a pair, unlike the dominant mutation.

(4) Senescence: state of a cell after a certain number of cell divisions have taken place (ageing).

(5) Linear energy transfer (LET): expression of the energy transferred to matter by radiation passing through it.

(6) Oncogene: a gene that favours cell modification, and so one of the many genes that contribute to the appearance of cancerous tumours.

(7) Meiosis: a cell division process specific to germinal cells, generating four haploid cells, the gametes.

not last beyond the seventh month in the female foetus. In males, the proliferation of the gonocytes lasts until the neonatal period. It then stops and resumes at puberty. Thus a high proportion of cell divisions precedes the formation of the gametes. In females, the number is estimated at 24 between the zygote (first cell) and the mature ovum. In males, some 30 divisions occur up until puberty, i.e., about age 15, and 23 per year thereafter. This makes about 150 divisions at age 20, 380 at age 30, and 600 at age 40. Thus for an average reproductive age of 30, the sex cells will have undergone 15 times more divisions in men than in women.

Because radiosensitivity, like sensitivity to **mutagens** in general, largely depends on the phase of the cell cycle, and so whether the cells are cycling or not, the number of mutations occurring in the male germinal line can be expected to be much higher than in the female line. This should result in *de novo* mutations being more frequently of male than of female origin, which is what indeed is observed.

After the proliferation step, the germinal cells have to undergo meiosis, a complex process that takes place differently according to the sex. Its purpose is dual: (i) it allows the intermingling of characters by recombination of homologous chromosomes and their independent segregation, and (ii) it reduces the genome to an array of haploid chromosomes so that diploidy(8) can be re-established after fertilisation.

The complexity of meiosis makes it by far the cell division responsible for the greatest number of chromosomal aberrations. A fraction of these aberrations is maintained until conception, a smaller fraction until the end of embryogenesis (third month of gestation) and an even smaller fraction (1 to 5%) until birth. Thus 30 to 40% of the products of conception may bear a chromosomal aberration. This proportion is only about 0.5% at birth.

Unlike mutations, chromosomal anomalies are much more often of maternal than paternal origin. The reason for this is probably the strong selection against male germinal cells with unbalanced genomes. The ovocyte does not undergo this counter-selection because its meiosis ends only at the time of fertilisation. Before the occurrence of any chromosomal aberrations, the mature ovocyte has thus built up reserves to enable the zygote to effect several divisions without synthesis. Thus both sexes contribute to the transmission of hereditary diseases, males mostly by gene mutations and females by chromosomal aberrations.

Survival beyond the differentiation phase allowing gametogenesis and the differentiation that follows the formation of the zygote have no equivalent in the somatic tissues. The remanence of the mutations and their ineluctable **expression** at some stage of *in utero* development or later in life make them particularly dangerous. Thus sexual reproduction is probably the most imperfect biological process because of the high number of errors it generates. Fortunately, most of these are eliminated by selection, but some are compatible with birth and life. The health disorders they entail may be medically and socially very onerous, however.

(8) Haploid/diploid: terms describing a cell with one/two sets of homologous chromosomes.

Hereditary health disorders

Hereditary diseases continue to attract increasing interest. This is partly due to the progress made in identifying rare syndromes, and partly to the recognition of a hereditary contribution in certain well-known late-onset health disorders.

Congenital hereditary health disorders (detectable at birth) are rare, but multiple. Of ranging seriousness, they affect about 9% of children. Single causes (monofactorial *i.e.* linked to damage to a single gene with no contribution from other factors) account for a minority of cases: dominant mutations 1.5%, autosomal recessive 0.75%, linked to the X chromosome 0.15% and by chromosomal aberration 0.4%. Diseases with multifactorial causes concern some 6% of children. It now appears that a large majority of the mutations reveal their pathological character only in adulthood, and sometimes late in life. They often act in a multifactorial context, making the subject more vulnerable to other factors, whether genetic or not. The types of disease concerned, such as diabetes, arterial hypertension, auto-immune diseases and high blood cholesterol are limited in number, but frequent, so that about 65% of the population is predisposed to developing one or more of these disorders.

It is noteworthy that certain pre-dispositions to cancer, completely unknown a few years ago, are among the most frequent single-cause adult diseases, with an **incidence** of 1 in 1,000 (breast cancer) to 5 in 1,000 (colonic cancer). All the hereditary cancers are catalogued in a reference work published under the editorship of V. Mc Kusick. In 2000, it listed 11,000 disorders, with average incidence values between 0.5 and $5 \cdot 10^{-5}$. In about 300 of them, the causative DNA damage was pinpointed by molecular studies. In the great majority of cases it was a point mutation (modification of a base) or a deletion.

The mutations affecting certain genes are targeted on one or more exons(9). These targeted mutations are often of dominant expression. Other mutations, on the contrary, are distributed over the whole gene. Their expression is often recessive.

As the concepts of dominance and recessiveness have become more complicated, the latest versions of Mc Kusick's catalogue no longer state these features, even though they are still of practical value. In 1994, out of 6,700 diseases, 67% were autosomal dominant, 25% autosomal recessive, 6% linked to the X chromosome, 0.3% linked to the Y chromosome and 0.9% of **mitochondrial** origin. Considering that the dominant mutations are mostly targeted and the recessive ones mostly randomly distributed over the genes, the fact that nearly three times more dominant hereditary diseases are recognised than recessive ones seems somewhat paradoxical. This anomaly is probably due to reporting bias.

(9) A gene is made up of coding sequences, the exons, that alternate with often longer non-coding sequences, the introns, in addition to regulating sequences.

Diseases with recessive transmission difficult to number

Four fifths of genetic disorders were identified in the last 30 years, whereas most of the other known diseases have been known for a very long time. This late identification is mainly due to the rarity of these disorders. A physician is unlikely ever to meet two similar cases in a lifetime, unless it is a familial recurrence. The probability of such a recurrence is high for dominant mutations or those linked to the X chromosome, but much lower for autosomal recessive mutations. This can explain why twice as many dominant as recessive hereditary diseases have been identified in the last 30 years. It is thus likely that a large proportion of rare diseases due to autosomal recessive transmission remain to be described. It is obviously important to be able to identify them to evaluate the potential effect of a mutagen. The human genome counts some 30,000 genes in all, two to three times fewer than previously estimated. The mutation of these genes does not necessarily cause a disease in every case. A mutation can be incompatible with cell survival or growth beyond the early embryo stage, and so go undetected. Or it can produce no effect recognised as pathological.

We do not yet know what proportion of our genes can produce a health disorder by mutation. The number is probably at least 11,000, the number of genetic disorders currently recorded. The data given above indicate that there are about 4.5 times more autosomal recessive diseases than those linked to the X chromosome. Out of a total of 2,907 million base pairs for the whole haploid genome, the X chromosome contains 128, i.e., 4.4%. If the genes that can produce a disease are evenly distributed over the **karyotype**, we would expect 25 times more autosomal diseases than those linked to the X chromosome.

Data on the genome do not yet provide answers to these questions concerning pathogenic mutation rates, but they give us indications of the gene density of each chromosome. Compared with the average of autosomes, the gene density of the X chromosome seems to be lower by about one quarter.

The low relative incidence of known autosomal recessive diseases may therefore have two possible origins: a high proportion of genes with pathogenic mutations on the X chromosome, or a severe under-estimation of the number of autosomal recessive diseases.

The first, albeit improbable, interpretation assumes an accumulation of genes on the X chromosome contrary to the selective pressure. As the unfavourable recessive mutations of the X chromosome are expressed in the male, evolution should have favoured the movement of such genes from the X chromosome to the autosomes and not the reverse. It is therefore more likely that rare autosomal diseases have not yet been fully enumerated. Assuming the same proportion of recessive autosomal diseases as X-linked diseases, then some 12,000 autosomal recessive diseases would be expected among a total of about 20,000 genetic disorders. On this assumption about two genes out of three have pathogenic potential. It is thus most likely that the number of autosomal recessive diseases has been strongly underestimated.

Radio-induced mutations and disease

The preceding analysis and calculations do not prove anything either way, but they underline the difficulties that subsist in describing the full extent of hereditary diseases.

Let us return to the main characteristics of radio-induced DNA damage:

It is randomly distributed along the DNA molecules and it comprises double strand breaks that generate deletions and chromosome rearrangements after faulty repair.

Cells carrying such anomalies should be strongly counter-selected, unless the induced mutations have a recessive expression (which should often be the case). The immediate first-generation effects should be imperceptible because it is extremely unlikely that the mutation of the same gene is induced in both gametes giving rise to a zygote.

The **ICRP**, which can hardly be suspected of seeking to minimise the health risks of radiation, considers today that the hereditary hazard is more theoretical than real, and that the risk is nil or imperceptible. Though surely possible, this is still surprising. So before rallying to this opinion, let us look closely at the supporting facts.

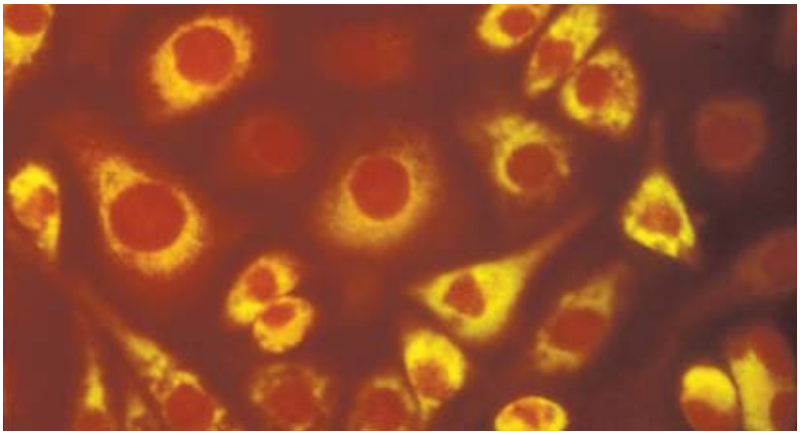
Hiroshima and Nagasaki: no evidence in three generations

No increase in hereditary diseases has been reported in the descendants of the survivors of the nuclear explosions. Nearly sixty years on, this means no detectable effects in first, second and third generations. The induction of dominant mutations or chromosomal aberrations compatible with embryonic and foetal survival can therefore be ruled out. But what about recessive mutations? A strong induction of such mutations would appreciably increase the frequency of heterozygous carriers, but outside incest, there is no more than the tiniest chance that the same recessive mutation has been transmitted to both members of a couple. Several generations are necessary for these mutations to spread throughout a population before they have a reasonable chance of become homozygous.

Hiroshima and Nagasaki do not, therefore, tell us anything yet about the hereditary risk by recessive mutations, which are those most likely to result from radiation.

Populations exposed to high natural radiation levels

There are several regions in the world where populations are exposed to high levels of natural radiation. This can be because of high altitude, where cosmic radiation is higher: this is the case for the Bolivian *altiplano*. It can also be because of high telluric radiation, such as in the Kerala coastal strip in southern India, which is rich in monazite. Here, on a limited territory a large sedentary population



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Chinese hamster ovary cells. Animal experiments have confirmed the rarity of dominant point mutations after irradiation.

has lived for at least 1,000 years, exposed to an annual radioactivity ranging from 1 to 40 mGy/year. The average reproductive age is 25 years, which represents a total pre-conceptional exposure of 0.025 to 1 Gy. **Dosimetric** and congenital malformation data have been collected in soundly-conducted studies since the eighties. To date, no effect has been demonstrated. This is precisely the type of data that needs to be exploited more thoroughly, and joint work with Indian scientists is being organised for this purpose.

Data from animal experimentation

Important experiments have been performed on the induction of mutations in mice. The aim was mainly to detect first-generation anomalies, assumed to correspond to dominant mutations. In fact, multiple phenotypic anomalies were detected, which could mostly be explained by anomalies at the chromosome scale, mainly deletions. These were thus haplo-insufficiency syndromes, well-known in man. This confirms the predictable rarity of dominant point mutations.
Other earlier experiments on generations of irradiated mice showed no effects. This could argue against the role of recessive mutations, but the analysis of the **phenotypes** was very summary. Considering the difficulty identifying hereditary diseases in man, we must be cautious in drawing any conclusions about such disorders in mice.

A knowledge gap

The risk of autosomal recessive hereditary diseases is thus still unknown. If we consider the theoretical calculations we can make to evaluate the spread of mutations in populations, assuming the risk exists, then there is some reason to fear a slow increase in rare hereditary disorders. In the present state of knowledge, it would be most useful to try to assess this risk. The example of Chernobyl shows that it is infinitely preferable to quantify a risk, even if it is very low, rather than to deny its existence. In the grey area between no risk and low risk, the public always sees an unknown and so a possibly high risk. This is why, difficult though it may be, this work is so important.

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A Natural and artificial radioactivity

Everything on the earth's surface has always been exposed to the action of ionising radiation from natural sources. Natural radiation, which accounts for 85.5% of total radioactivity (natural plus artificial), is made up of 71% telluric radiation and about 14.5% cosmic radiation. The radionuclides formed by the interaction of **cosmic rays** arriving from stars, and especially the Sun, with the nuclei of elements present in the atmosphere (oxygen and nitrogen) are, in decreasing order of dose (Box F, *From rays to dose*) received by the population, carbon-14, beryllium-7, sodium-22 and tritium (hydrogen-3). The last two are responsible for only very low doses.

Carbon-14, with a half life of **5,730 years**, is found in the human body. Its activity per unit mass of carbon has varied over time: it has diminished as carbon dioxide emissions from the combustion of fossil fuels have risen, then was increased by atmospheric nuclear weapon tests.

Beryllium-7, with a half life of **53.6 days**, falls onto the leaf surfaces of plants and enters the body by ingestion (Box B, *Human exposure routes*). About 50 Bq (becquerels) per person per year of beryllium-7 are ingested.

The main or **"primordial" radionuclides** are potassium-40, uranium-238 and thorium-232. Along with their radioactive decay products, these elements are present in rocks and soil and are therefore found in many building materials. Their concentrations are generally very low, but vary according to the nature of the mineral. The gamma radiation emitted by these radionuclides forms the **telluric radiation**, which is responsible for the external exposure of the body. The primordial radionuclides and many of their long-lived descendants are also found in trace amounts in drinking water and plants: this results in an internal exposure by ingestion, plus an additional low exposure by inhalation of airborne suspended dust particles.

Potassium-40 is a beta and gamma emitter with a half life of **1.2 thousand million years**, and has no radioactive descendants. This radioactive isotope makes up 0.0118% of all natural potassium, and enters the body by ingestion. The mass of natural potassium in the human body is independent of the quantity ingested.

Uranium-238 is an alpha emitter with a half life of **4.47 thousand million years**. It has thirteen main alpha-, beta- and gamma-emitting radioactive descendants, including **radon-222** (**3.82 days**) and **uranium-234** (**0.246 million years**). Uranium-238 and its two descendants **thorium-234** (**24.1 days**) and **protactinium-234m**(1) (**1.18 min**), and **uranium-234** are essentially incorporated by ingestion and are mainly concentrated in the bones and kidneys.

Thorium-230, derived from uranium-234, is an alpha emitter with a period of **80,000 years**. It is an osteotrope, but enters the body mainly by the pulmonary route (inhalation). **Radium-226**, a descendant of thorium-230, is an alpha emitter with a half life of **1,600 years**. It is also an osteotrope and enters the body mainly *via* food. Another osteotrope, **lead-210** (**22.3 years**), is incorporated by inhalation though mostly by ingestion.

Thorium-232 is an alpha emitter with a half life of **14.1 thousand million years**. It possesses ten main alpha-, beta- and gamma-emitting radioactive descendants including **radon-220** (**55 s**). Thorium-232 enters the body mainly by inhalation. **Radium-228**, a direct descendant of thorium-232, is a beta-emitter with a half life of **5.75 years**. It enters the body mainly in food.

Radon, a gaseous radioactive descendant of uranium-238 and thorium-232, emanates from the soil and building materials, and along with its short-lived alpha-emitting descendants constitutes a source of internal exposure through inhalation. Radon is the most abundant source of natural radiation (about 40% of total radioactivity).

The human body contains nearly 4,500 Bq of potassium-40, 3,700 Bq of carbon-14 and 13 Bq of radium-226 essentially imported in food.

Natural radiation is supplemented by an anthropic component, resulting from the medical applications of ionising radiation and to a lesser extent from the nuclear industry. It accounts for about 14.5% of the total radioactivity worldwide, but much more in the developed countries. In the medical field (more than 1 mSv/year on average in France), irradiation by external sources predominates: radiodiagnosis (X-rays) and radiotherapy, long based on cæsium-137 and cobalt-60 sources, but now more and more often using linear accelerators. Irradiation by internal routes (curietherapy with iridium-192) has more specialised indications (cervical cancer, for example). The metabolic and physicochemical properties of some twenty radionuclides are put to use for **medical activities** and in **biological research**. The medical applications comprise radiodiagnostics (scintigraphy and radio-

(1) m for metastable. A nuclide is said metastable when a transition delay exists between the excited state of the atom and the stable one.

immunology), and treatment, including thyroid disorders using iodine-131, radioimmunotherapy in certain blood diseases (phosphorus-32) and the treatment of bone metastasis with strontium-89 or radiolabelled phosphonates alongside other uses of radiopharmaceuticals. Among the most widely used radionuclides are: **technetium-99m** (half life **6.02 hours**) and **thallium-201** (half life **3.04 days**) (scintigraphy), **iodine-131** (half life **8.04 days**) (treatment of hyperthyroidism), **iodine-125** (half life **60.14 days**) (radioimmunology), **cobalt-60** (half life **5.27 years**) (radiotherapy), and **iridium-192** (half life **73.82 days**) (curietherapy). The average contribution of radiological examinations to total radioactivity amounts to 14.2%.

The **early atmospheric nuclear weapon tests** scattered fallout over the whole of the earth's surface and caused the exposure of populations and the contamination of the food chain by a certain number of radionuclides, most of which, given their short radioactive half lives, have now vanished. There remain **cæsium-137** (**30 years**), **strontium-90** (**29.12 years**), some **krypton-85** (**10.4 years**) and **tritium** (**12.35 years**), and the isotopes of **plutonium** (half lives **87.7 years** to **24,100 years**). Currently, the doses corresponding to the fallout from these tests are essentially attributable to fission products (cæsium-137) and to carbon-14, rather than activation products and plutonium.

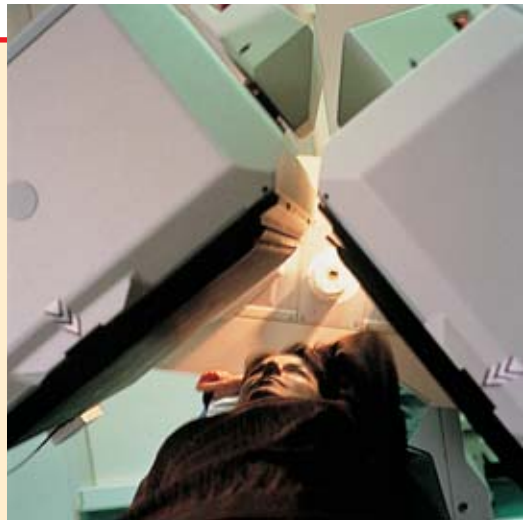
In the **Chernobyl accident** (Ukraine), which occurred in 1986, the total radioactivity dispersed into the atmosphere was of the order of 12 milliard milliard (10^{18}) becquerels over a period of 10 days. Three categories of radionuclides were disseminated. The first consisted of volatile fission products such as **iodine-131**, **iodine-133** (**20.8 hours**), **cæsium-134** (**2.06 years**), **cæsium-137**, **tellurium-132** (**3.26 days**). The second was composed of solid fission products and actinides released in much smaller amounts, in particular the strontium isotopes ^{89}**Sr** (half life **50.5 days**) and ^{90}**Sr**, the ruthenium isotopes ^{103}**Ru** (half life **39.3 days**) and ^{106}**Ru** (half life **368.2 days**), and **plutonium-239** (**24,100 years**). The third category was rare gases which although they represented most of the activity released, were rapidly diluted in the atmosphere. They were mainly **xenon-133** (**5.24 days**) and **krypton-85**.

The contributions of the early atmospheric nuclear weapon tests and the Chernobyl accident to the total radioactivity are roughly 0.2% (0.005 mSv) and 0.07% (0.002 mSv) respectively.

The whole of the **nuclear-powered electricity production** cycle represents only about 0.007% of total radioactivity. Almost all the radionuclides remain confined inside the nuclear reactors and the fuel cycle plants. In a nuclear reactor, the reactions that take place inside the fuel yield transuranics. **Uranium-238**, which is non-fissile, can capture neutrons to give in particular plutonium isotopes ^{239}**Pu**, ^{240}**Pu** (half life **6,560 years**) and ^{241}**Pu** (half life **14.4 years**), and **americium-241** (**432.7 years**). The main fission products generated by the fission of **uranium-235** (**704 million years**) and **plutonium-239** are **iodine-131**, **cæsium-134**, **cæsium-137**, **strontium-90** and **selenium-79** (**1.1 million years**).

The main radionuclides present in releases, which are performed in a very strict regulatory framework are, in liquid release, **tritium**, **cobalt-58** (**70.8 days**), **cobalt-60**, **iodine-131**, **cæsium-134**, **cæsium-137** and **silver-110m** (**249.9 days**). In gaseous releases **carbon-14** is the most abundant radionuclide, emitted most often as carbon dioxide. In all the reactors in the world, the total production of radiocarbon dioxide amounts to one tenth of the annual production formed naturally by cosmic radiation.

In addition, certain radionuclides related to the nuclear industry exhibit chemical toxicity (Box D, *Radiological and chemical toxicity*).



Laurence Médard/CEA

Classical scintigraphy performed at the Frédéric-Joliot Hospital Service (SHFJ). The gamma-ray camera is used for functional imaging of an organ after administration, usually by the intravenous route, of a radioactive drug (radiopharmaceutical) to the patient. The radionuclides used are specific to the organ being studied: for example, technetium-99m for the kidneys and bones, thallium-201 for the myocardium. The injected radiopharmaceutical emits gamma photons, which are captured by two planar detectors placed at 180° or 45° according to the examination.

B Human exposure routes

Human **exposure**, i.e., the effect on the body of a chemical, physical or radiological agent (irrespective of whether there is actual contact), can be external or internal. In the case of **ionising radiation**, exposure results in an energy input to all or part of the body. There can be direct **external irradiation** when the subject is in the path of radiation emitted by a radioactive source located outside the body. The person can be irradiated directly or after reflection off nearby surfaces.

The irradiation can be **acute** or **chronic**.

The term **contamination** is used to designate the deposition of matter (here **radioactive**) on structures, surfaces, objects or, as here, a living organism. Radiological contamination, attributable to the presence of **radionuclides**, can occur by the **external** route from the receptor medium (air, water) and vector media (soils, sediments, plant cover, materials) by contact with skin and hair (cutaneous contamination), or by the **internal** route when the radionuclides are **intaken**, by **inhalation** (gas, particles) from the atmosphere, by **ingestion**, mainly from foods and beverages (water, milk), or by penetration (injury, burns or diffusion through the skin). The term **intoxication** is used when the toxicity in question is essentially chemical.

In the case of **internal contamination**, the dose delivered to the body over time (called the **committed dose**) is calculated for 50 years in adults, and until age 70 years in children. The parameters taken into account for the calculation are: the nature and the intaken quantity of the radionuclide (RN), its chemical form, its **effective half life**[1] in the body (combination of **physical** and **biological half lives**), the type of **radiation**, the mode of exposure (inhalation, ingestion, injury, transcutaneous), the distribution in the body (deposition in target organs or even distribution), the radiosensitivity of the tissues and the age of the contaminated subject.

Lastly, the **radiotoxicity** is the toxicity due to the ionising radiation emitted by the inhaled or ingested radionuclide. The misleading variable called **potential radiotoxicity** is a *radiotoxic inventory* that is difficult to evaluate and made imprecise by many uncertainties.

(1) The effective half life (Te) is calculated from the physical half life (Tp) and the biological half life (Tb) by $1 / Te = 1 / Tp + 1 / Tb$.

F From rays to dose

Radioactivity is a process by which certain naturally-occurring or artificial **nuclides** (in particular those created by **fission**, the splitting of a heavy nucleus into two smaller ones) undergo spontaneous **decay**, with a release of energy, generally resulting in the formation of new nuclides. Termed **radionuclides** for this reason, they are unstable owing to the number of nucleons they contain (protons and neutrons) or their energy state. This decay process is accompanied by the emission of one or more types of **radiation**, ionising or non-ionising, and (or) particles. **Ionising radiation** is electromagnetic or corpuscular radiation that has sufficient energy to ionise certain atoms of the matter in its path by stripping electrons from them. This process can be *direct* (the case with alpha particles) or *indirect* (gamma rays and neutrons).

Alpha radiation, consisting of helium-4 nuclei (two protons and two neutrons), has low penetrating power and is stopped by a sheet of paper or the outermost layers of the skin. Its path in biological tissues is no longer than a few tens of micrometres. This radiation is therefore strongly ionising, i.e., it easily strips electrons from the atoms in the matter it travels through, because the particles shed all their energy over a short distance. For this reason, the hazard due to radionuclides that are **alpha emitters** is **internal exposure**.

Beta radiation, made up of electrons (beta minus radioactivity) or positrons (beta plus radioactivity), has moderate penetrating power. The particles emitted by **beta emitters** are stopped by a few metres of air, aluminium foil, or a few millimetres of biological tissue. They can therefore penetrate the outer layers of the skin.

Gamma radiation composed of high energy photons, which are weakly ionising but have high penetrating power (more than the **X-ray** photons used in radiodiagnosis), can travel through hundreds of meters of air. Thick shielding of concrete or lead is necessary to protect persons.

The interaction of **neutron radiation** is random, and so it is stopped only by a considerable thickness of concrete, water or paraffin wax. As it is electrically neutral, a neutron is stopped in air by the nuclei of light elements, the mass of which is close to that of the neutron.

• The quantity of energy delivered by radiation is the **dose**, which is evaluated in different ways, according to whether it takes into account the quantity of energy absorbed, its rate of delivery, or its biological effects.

• The **absorbed dose** is the quantity of energy absorbed at a point per unit mass of matter (inert or living), according to the definition of the International Commission on Radiation Units and Measurements (**ICRU**). It is expressed in **grays** (Gy): 1 gray is equal to an absorbed energy of 1 joule per kilogramme of matter. The *organ absorbed dose* is obtained by averaging the doses absorbed at different points according to the definition of the International Commission on Radiological Protection (**ICRP**).

• The **dose rate**, dose divided by time, measures the intensity of the irradiation (energy absorbed by the matter per unit mass and per unit time). The legal unit is the gray per second (Gy/s), but the gray per minute (Gy/min) is commonly used. Also, radiation has a higher **relative biological effectiveness (RBE)** if the effects produced by the same dose are greater or when the dose necessary to produce a given effect is lower.

• The **dose equivalent** is equal to the dose absorbed in a tissue or organ multiplied by a **weighting factor**, which differs according to the nature of the radiation energy, and which ranges from 1 to 20. Alpha radiation is considered to be 20 times more harmful than gamma radiation in terms of its biological efficiency in producing random (or **stochastic**) effects. The equivalent dose is expressed in sieverts (Sv).

• The **effective dose** is a quantity introduced to try to evaluate harm

Foulon/CEA

Technicians operating remote handling equipment on a line at the Atalante facility at CEA Marcoule. The shielding of the lines stops radiation. The operators wear personal dosimeters to monitor the efficacy of the protection.

in terms of whole-body stochastic effects. It is the sum of *equivalent doses* received by the different organs and tissues of an individual, weighted by a factor specific to each of them (weighting factors) according to its specific sensitivity. It makes it possible to sum doses from different sources, and both external and internal radiation. For internal exposure situations (**inhalation**, **ingestion**), the effective dose is calculated on the basis of the number of **becquerels** incorporated of a given radionuclide (**DPUI**, **dose per unit intake**). It is expressed in sieverts (Sv).

• The **committed dose**, as a result of internal exposure, is the cumulated dose received in fifty years (for workers and adults) or until age 70 (for those aged below 20) after the year of **incorporation** of the radionuclide, unless it has disappeared by physical shedding or biological elimination.

• The **collective dose** is the dose received by a population, defined as the product of the number of individuals (e.g., those working in a nuclear plant, where it is a useful parameter in the optimisation and application of the ALARA system) and the average equivalent or effective dose received by that population, or as the sum of the individual effective doses received. It is expressed in man-sieverts (man.Sv). It should be used only for groups that are relatively homogeneous as regards the nature of their exposure.

D Radiological and chemical toxicity

The chemical toxics linked to the nuclear industry include **uranium** (U), **cobalt** (Co), **boron** (B), used for its neutron-absorbing properties in the heat-exchange fluids of nuclear power plants, **beryllium** (Be), used to slow neutrons, and **cadmium** (Cd), used to capture them. Boron is essential for the growth of plants. Cadmium, like lead (Pb), produces toxic effects on the central nervous system. When the toxicity of an element can be both radiological and chemical, for example that of plutonium (Pu), uranium, neptunium, technetium or cobalt, it is necessary whenever possible to determine what toxic effects are radiological, what are chemical, and what can be either radiological or chemical (see *Limits of the comparison between radiological and chemical hazards*).

For **radioactive** elements with long physical **half lives**, the chemical toxicity is a much greater hazard than the radiological toxicity, as exemplified by rubidium (Rb) and natural uranium. Thus the chemical toxicity of uranium, which is more important than its radiological toxicity, has led the French regulators to set the **ingested** and **inhaled** mass limits for uranium in chemical compounds at 150 mg and 2.5 mg per day respectively, regardless of the **isotopic** composition of the element.

Certain metals or **metalloids** that are non-toxic at low concentrations can become toxic at high concentrations or in their radioactive form. This is the case for cobalt, which can be **genotoxic**, selenium (Se) (naturally incorporated in **proteins** or **RNA**), technetium (Tc) and iodine (I).

Cyrille Dupont/CEA

Two-dimensional gel electrophoresis image analysis carried out in the course of nuclear toxicology work at CEA Marcoule Centre in the Rhone Valley.