III. LATE RESPONSES

Cancer: evidence that the defenses have failed

In humans, the cells of a healthy individual divide only under the control of the neighboring cells. But cancer cells ignore extracellular signals and keep to their own duplication program. All the cells of a tumor are descended from a single uncontrolled cell that has divided and grown into a tumoral clone. This gradual process, which can take years or even decades, results from mutations accumulated in certain genes of the rogue cell.

Two classes of genes, the proto-oncogenes and the tumor suppressor genes, code for proteins involved in the regulation of the cell division cycle, and are fundamental role to the onset of cancer. The first class stimulates cell growth, and the second slows it. A chromosome fragment bearing a tumor suppressor gene can be lost (or deleted) by a break in the two DNA strands due to ionization radiation or some other mutagenic agent. This deletion may then impair a mechanism that arrests cell division. Genes coding for repair systems are also implicated in cancer growth. Mutations in these genes make the DNA unstable, and the tumor cells will contain inconsistently repaired DNA, differing from one cell to another.

DNA damage, oncogene activation or inactivation of a tumor suppressor gene normally causes the cell to commit suicide. The tumoral clone thus comes from a cell that has somehow escaped this programmed death. The second defense mechanism that cells have against uncontrolled proliferation is linked to the shortening, at each duplication, of the DNA segments, or telomeres, at the chromosome ends. This clipping is a record of the number of cell divisions. When the telomeres get too short they no longer protect the ends of the chromosomes, and these then tend to fuse together. This generates unstable chromosomes, and the resulting disorder soon kills the cell. Telomerase, an enzyme that replaces the telomere segments shed at every division, is seldom found in healthy cells yet it is present in almost all tumor cells. A cell can thus be made immortal by modification of the gene coding for this enzyme.

All the cells in higher organisms contain two sets of homologous chromosomes, and therefore two copies of each gene. Cancer can only happen if both copies of the same gene, for example a tumor suppressor, mutate. A tumor therefore develops in stages, appearing only when several genes have mutated. This accounts for the long lag time between an initial mutation and later clonal evolution.

Sex cells have only one set of chromosomes, so that when an ovum and a spermatozoon combine they produce an egg with two sets. A localized mutation in the genetic heritage of a sex cell can therefore be passed down from one generation to the next. All the cells of the descendents will thus carry the mutation, because an individual grows by successive cell divisions, with DNA copied from the fertilized egg. People who inherit a mutant gene from a parent are thus more prone to cancer as tumoral clones form earlier.

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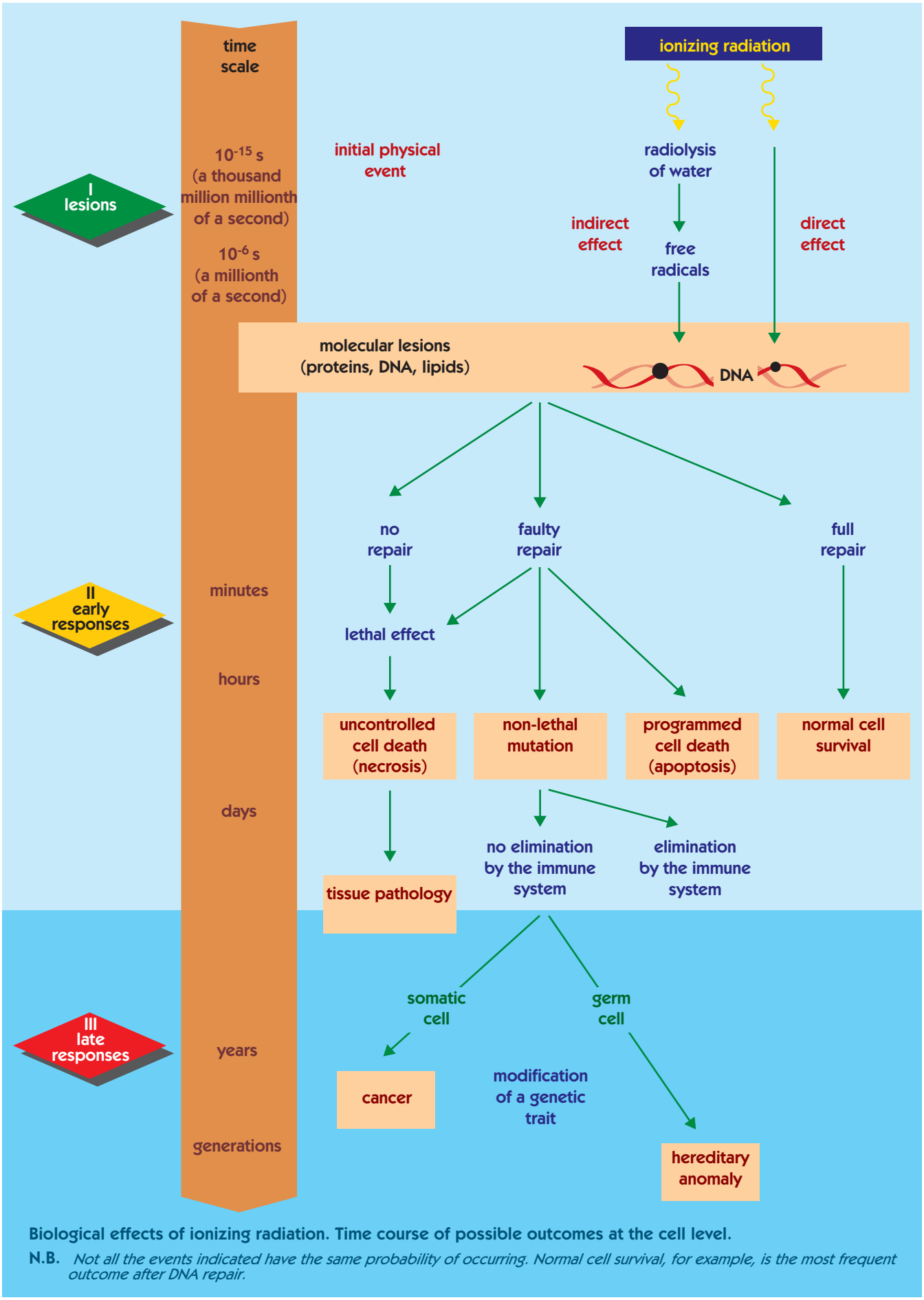

Biological effects of ionizing radiation. Time course of possible outcomes at the cell level.

N.B. *Not all the events indicated have the same probability of occurring. Normal cell survival, for example, is the most frequent outcome after DNA repair.*