



Direction Production Ingénierie



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CENTRE D'EXPERTISE ET D'INSPECTION DANS LES DOMAINES DE LA RÉALISATION ET DE L'EXPLOITATION

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Views on emerging scientific and societal issues in Radiological Protection

Individual radiosensitivity and screening tests in the workplace



Definition of a genetic test

- A genetic test is the analysis of human DNA, RNA, chromosomes, proteins, and certain metabolites in order to detect heritable disease-related genotypes, mutations, phenotypes or karyotypes for clinical purposes.

(US National Institute of Health Task Force)

A little history...about genetic testing

- 1970: In the United States, some employers screened for sickle-cell anemia (mutation of the hemoglobin S gene) in African Americans, most often without their consent.
 - ✦ Those carrying the mutation were not hired, although they were in good health and at no risk of developing the disease.
⇒ Indignant reactions in the US press
- In 1989, 5% of 330 US organizations surveyed (private companies, industrial groups, and trade unions) admitted genetic screening and surveillance of their employees.
- Another survey showed that 15% of 400 companies insured by Northwestern National Life Insurance planned within the next 10 years to **extend screening at hiring** not only to job applicants **but also to members of their family**.

An ethical issue

- Test demanded by a Texas railroad company to determine if its workers had a genetic predisposition to carpal tunnel syndrome, induced by repetitive wrist movement at work.
 - **An employee of 45 years refused the test and was fired.**
 - **A US government commission (Equal Employment Opportunity Commission) filed a court action to ban genetic tests on employees without their consent.**
- Determination of a genetic profile might be praiseworthy if it involved protecting future employees from risks to which they are more susceptible than others,
- but it opens the door to discrimination at work because it can be used for selecting employees without any certainty that it will lead to disease.
 - **Predictive medicine is not preventive medicine.**

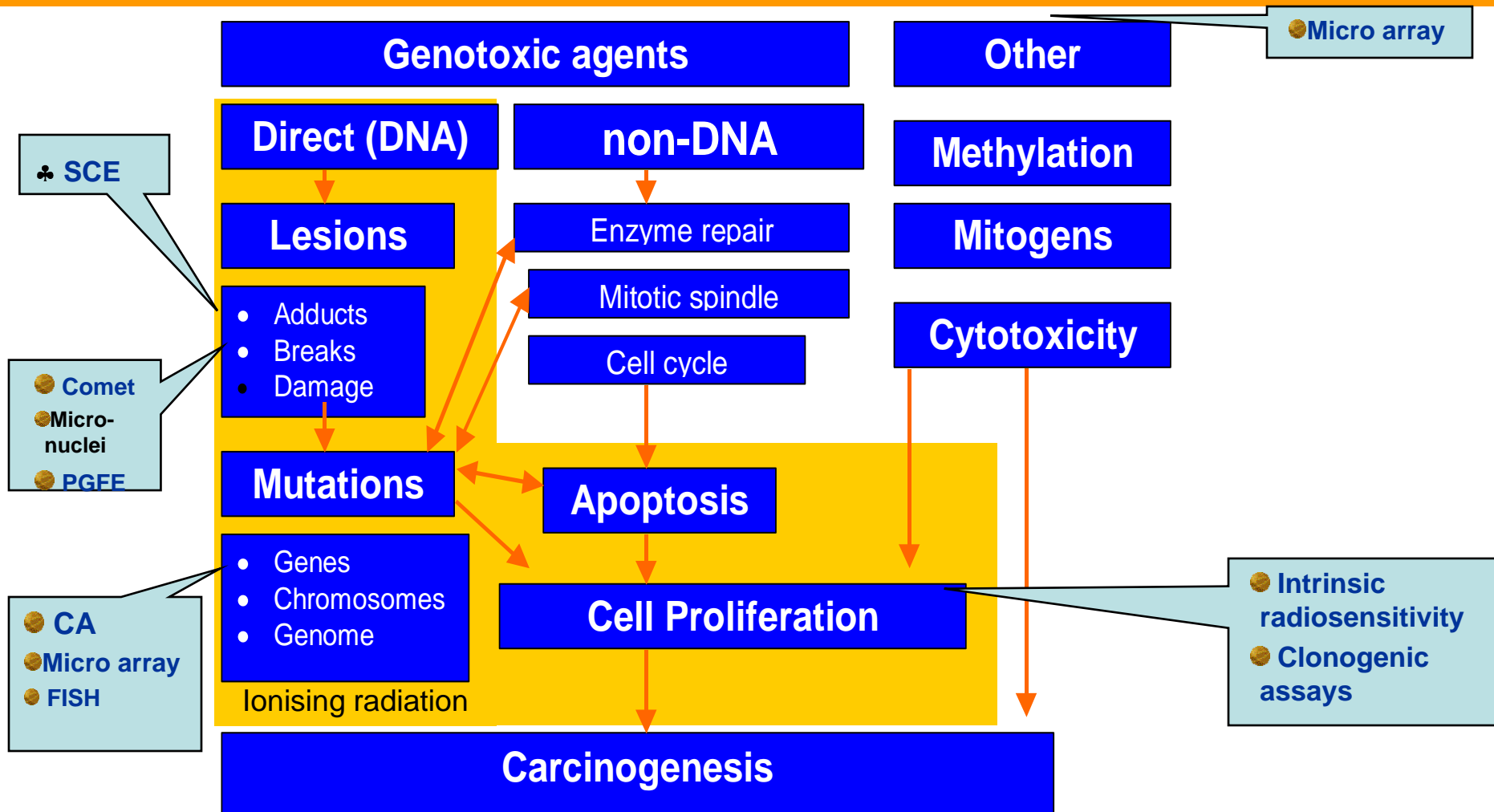
Who Wants to be a Millionaire?



❖ Definition of Radiosensitivity:

- A) Variable treatment response in patients receiving radiation therapy
- B) Reaction of healthy tissue after radiation therapy
- C) Intraindividual cell response variability according to dose and dose rate
- D) Interindividual variability in repairing DNA lesions or eliminating damaged cells
- E) Subjects more predisposed to radiation-induced tumors than the general population

MECHANISMS THAT INDUCE CARCINOGENESIS



PREVENTIVE MEDICINE: Genotoxicity BIOMONITORING

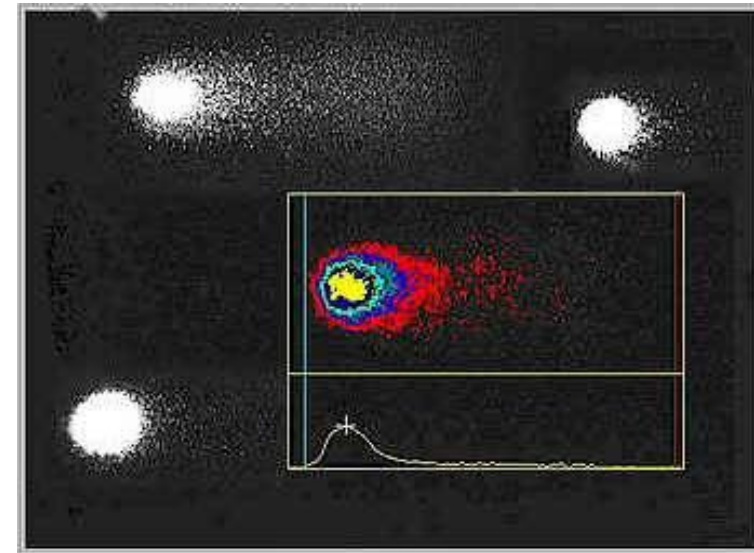
- ❖ **Genotoxicity tests of reversible damage**
 - sister chromatid exchange (SCE)
 - single-strand DNA breaks (comet assay)
 - gene induction/repression (Microarrays)
- ❖ **Genotoxicity tests of stable lesions**
 - mutation, eg, HGPRT for butadiene exposure
 - minisatellite instability
 - chromosomal aberration
 - clastogen/binuclear cell (micronuclei (MN) test)
- ❖ **Genotoxic exposure indicators**
- ❖ **Evidence of genotoxic effects**

IDEAL TEST IN PREVENTIVE MEDICINE

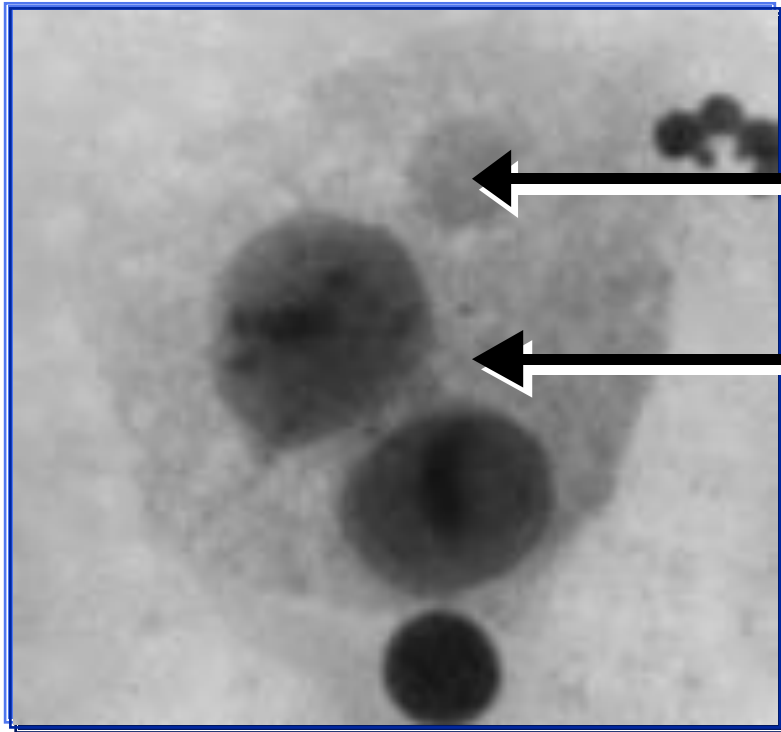
- reproducible - reference curves
- analyzes representative type of tissues
- kinetics: duration of lesions
- specific: confounding factors
 - **smoking, alcohol, drugs, dietary habits, recent radiologic examinations and endogenous factors**
- can be automated
- rapid

COMET ASSAY : can we use it in case of predictive medicine?

- ❖ Quantification of single/double strand DNA breaks after *in vitro* T lymphocyte exposure
- ❖ AT HIGH DOSES
 - detects subjects at risk of developing radiation-induced tumors (Leprat et al)
 - detects subjects with severe reactions to radiation therapy (Alapetite et al)
 - detects subjects with a genetic susceptibility to lung cancer (Zhang et al)
- ❖ Results: in 2 days



Example: MicroNuclei Test

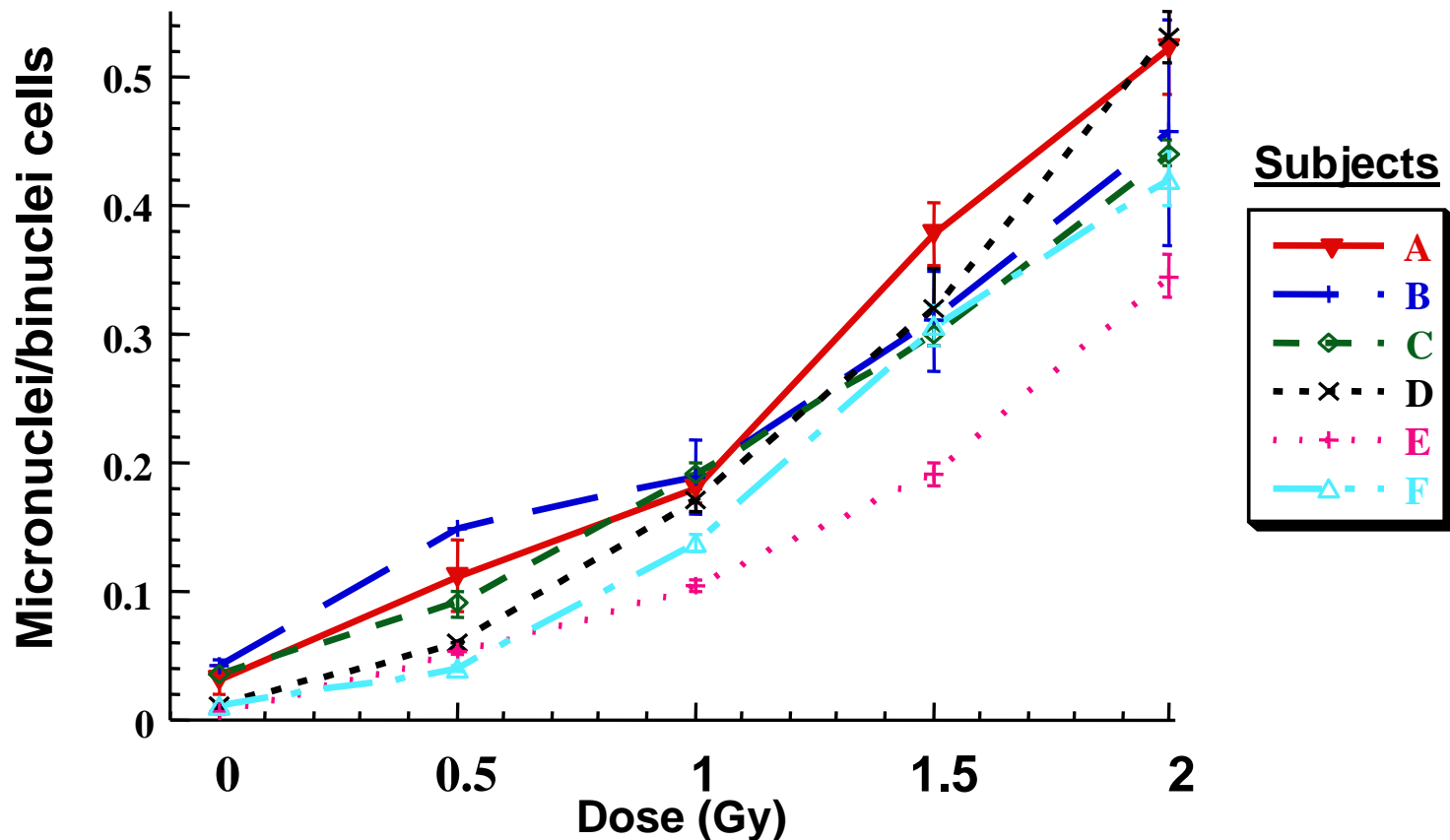


Micronucleus
Chromosome fragment

Binuclear cell

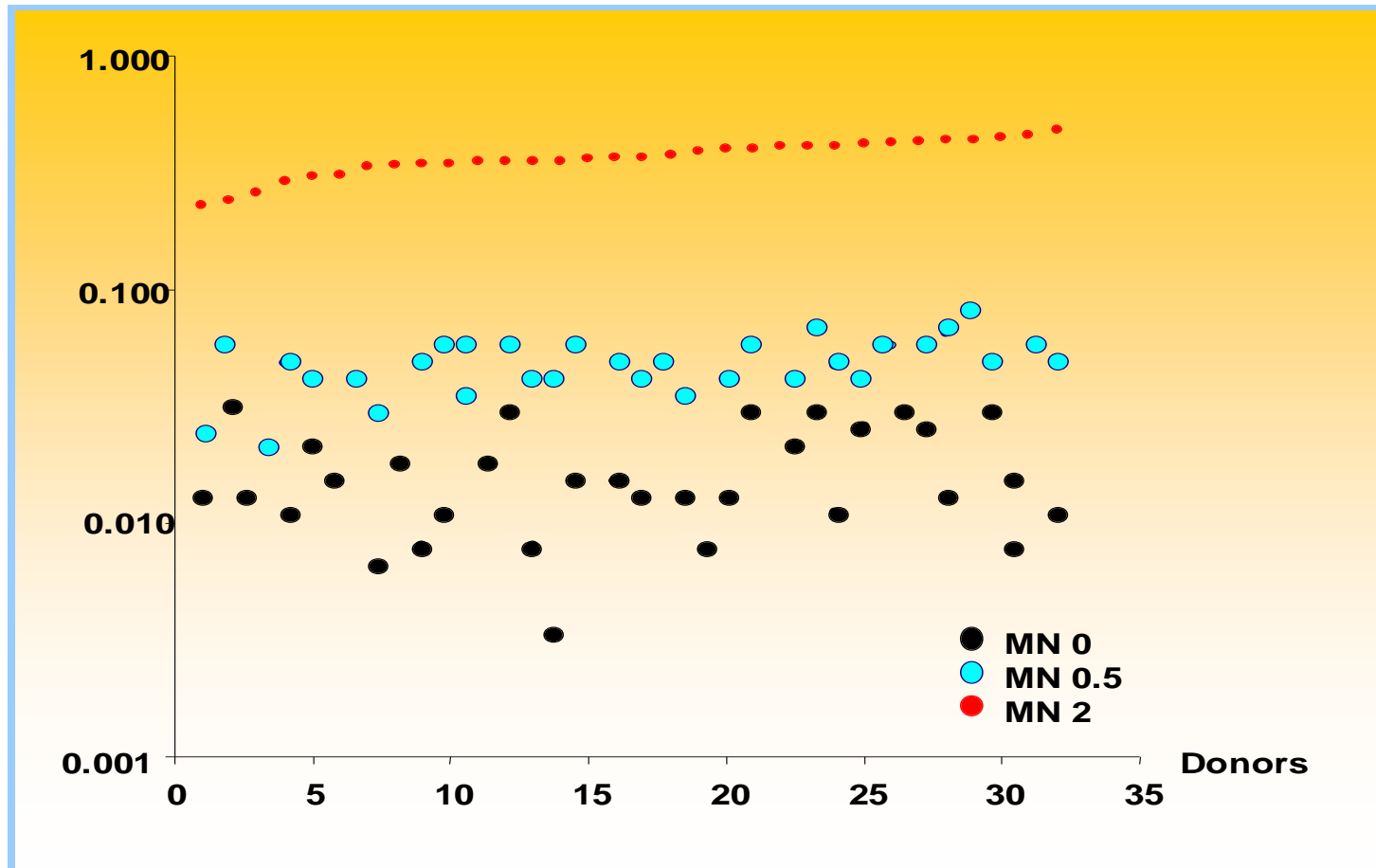
INTRA- AND INTERINDIVIDUAL VARIABILITY

In vitro micronuclei test for 6 healthy donors (CEA-DSV)



- Frequency of micronuclei induced in T lymphocytes of 6 healthy donors (A-F) after ex vivo irradiation (0.5, 1, 1.5 and 2 Gy). For each donor and each dose, the uncertainty bar represents the mean of 3 experiments.

VARIABILITY OF INDIVIDUAL RADIOSENSITIVITY



conclusion

- Genetic and epigenetic factors can modify or modulate gene expression as well as the synthesis, function and stability of proteins.
- Basal expression of some genes that repair DNA lesions and regulate the cell cycle predict the radiosensitivity
 - The difficulty is not test results but interpretation in term of consequences for the cell

Low doses of gamma irradiation (10 mGy) elicit different gene sets than high doses (2 Gy) in normal human skin cells

(Franco N. et al. Radiat. Res. 2005; 163: 623-635)

- Specific molecular responses are triggered in cultured primary keratinocytes from adult skin at high (2 Gy) or low (10 mGy) doses of gamma rays.



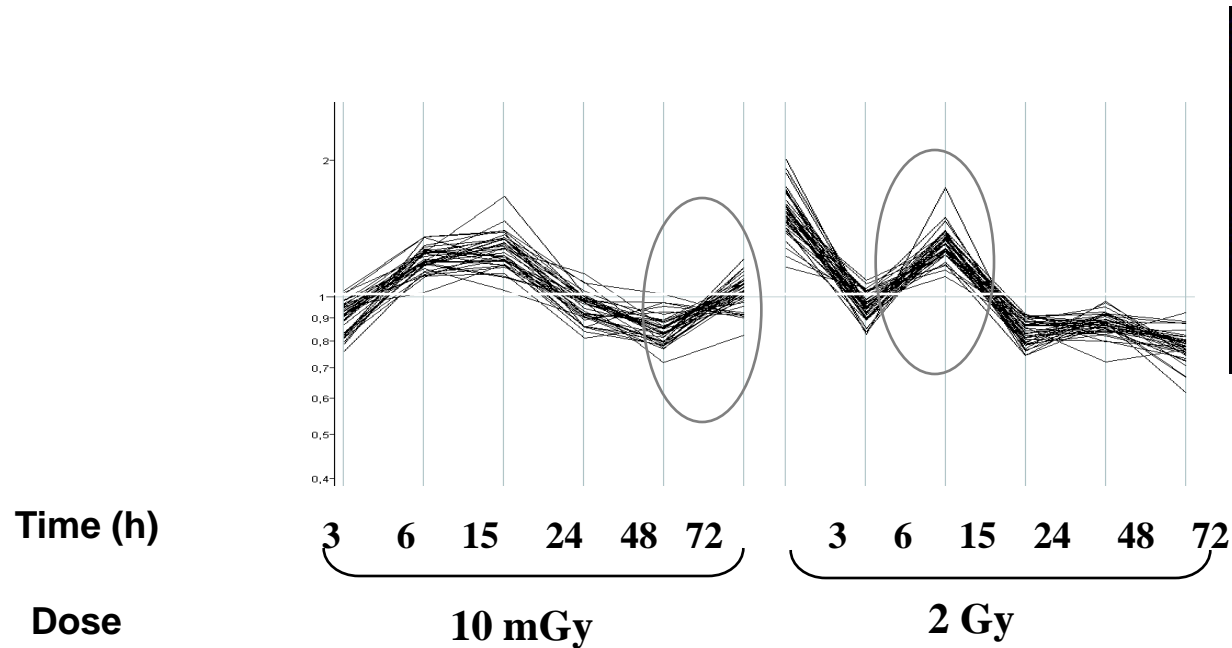
- Experiments with DNA microarrays (10,500 gene probes) show that among 853 modulated probes, **the expression of 214** are specifically modulated by low-dose (10 mGy) and **370 genes** by high-dose (2Gy) exposure.

- **Low-dose-specific genes** (140 known genes) include mostly genes of homeostasis, **cell communication**, **signaling**, membrane, cytoskeleton, RNA and protein synthesis, chromatin, energy metabolism, **stress**, cell death and transport but rarely DNA repair genes.

Conclusion ==> Radiation response at low doses is quite specific and different from that obtained at high doses.

Cluster analysis

- **38 genes:** regulation over 3 days



Conclusion

- After irradiation, some genes are neither induced nor suppressed,
- some are modulated by low doses, others are induced or suppressed only at a specific dose level.
 - Moreover they all differ according to dose and probably also according to dose rate.
- These results show that
 - the study of radiosensitivity (cellular response to irradiation) is complex, and
 - the response differs over time according to dose.

Variations in DNA repair efficiency

- **depend on genetic background**
 - individual hypersensitivity due to mutations or polymorphism of DNA repair genes in the general population (OGG1, XRCC1, etc.)
 - defects in damage **signaling and repair** are often associated with predisposition to cancer:
 - ATM==> lymphoma, breast cancer
 - BRCA1/BRCA2 ==> breast and ovarian cancer
 - Lig.IV---> immune deficiency
- **depend on the differentiation status of cells and tissue**
- **depend on age**

Individual sensitivity and polymorphisms in DNA repair genes

Individual sensitivity is rare and usually not detectable in population studies (epidemiology).

- Some patients undergoing radiodiagnostic examinations (eg, CT) or radiation therapy have been found to have decreased capacity for DSB repair (see, eg, Löbrich et al. 2005: PNAS)
- Several other studies point to the involvement of repair gene polymorphisms such as XRCC3, XRCC1 and XPD in the accumulation of genetic effects (micronuclei) in individuals chronically exposed to IR.

- a question of dose
- **XRCC1** and **glutathione-S-transferase gene polymorphisms** are associated with radiotherapy-related malignancies in survivors of Hodgkin disease (Mertens et al. Cancer 2004) so **for high dose received.**

GENETIC SCREENING TESTS AND IONIZING RADIATION

YES

YES

❖ **Genetically predisposed group:**

- Impaired capacity for DNA repair
- Rare diseases: AT (Ataxia Telangiectasia)
Fanconi anemia
NBS (Nijmegen breakage syndrome)
- Genetic predisposition to cancer (BRCA1 and 2)

● **Cytogenetic tests: YES**

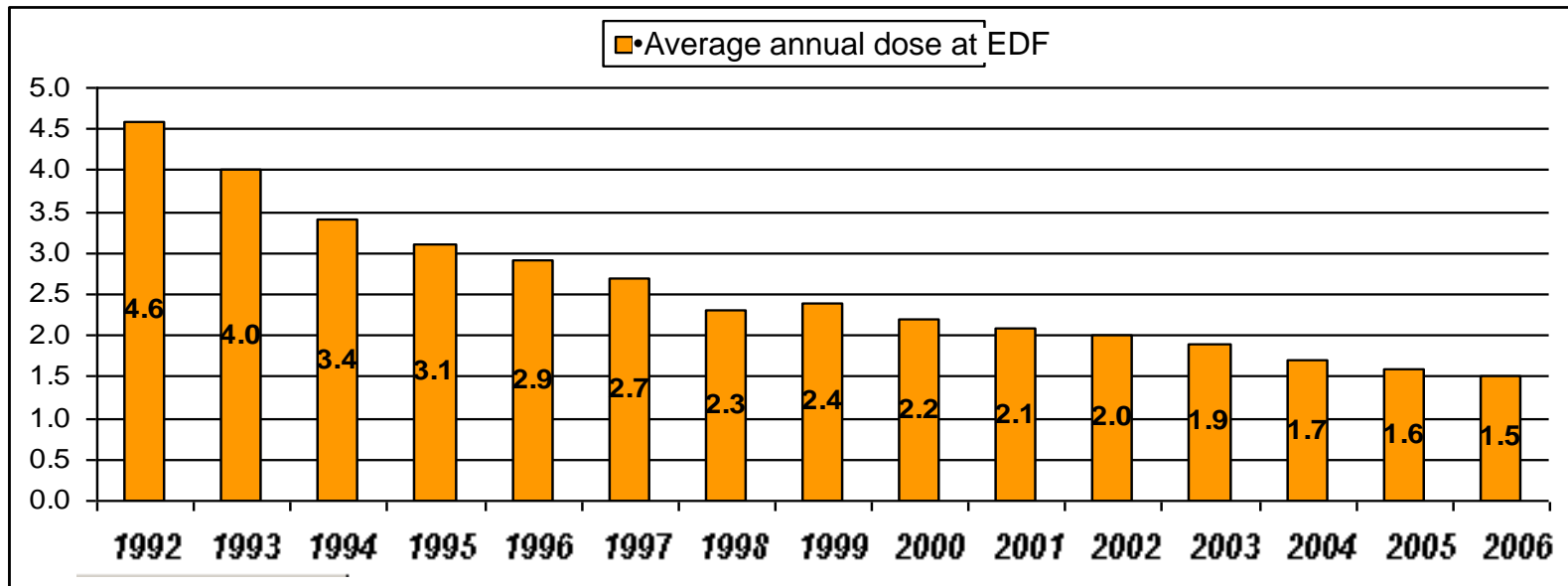
● **Indication: Optimization of therapeutic protocols using high-dose irradiation.**

INDICATION FOR PREDICTIVE TESTS IN OCCUPATIONAL MEDICINE?

NO

NO

- Exposed population \neq general population
- Genetic diseases involved: rare
- Level of occupational exposure: slight
- Improvement in radiation protection



Risk of genetic tests

- All these examples illustrate the limits in employment and the inevitable risk of abuse when employers can use their employees' medical data.
 - 17% of people surveyed in one US study preferred to conceal their genetic history from their employer, for fear that it would be used to discriminate against them.
- There is currently no federal law in the US that protects against the abuse of genetic screening or genetic information collection.
 - The real problem lies in the power of US employers combined with their obligation to pay most of their workers' payroll taxes and health insurance (in contrast to European employers).

What is the situation in France?

- A clear ambiguity between the bioethics law and labor law remains.
 - According to Act 94-654 dated 29 July 1994 on bioethics and to the Public Health Code, **a person's genetic characteristics can be examined only for medical or scientific research purposes and only after the person's written consent; violations are subject to sanctions under in the Penal Code.**
- but the labor law authorizes occupational physicians
 - "to prescribe addition examinations necessary to determine medical aptitude for the job and especially **to screen for condition presenting a contraindication to the job and to screen for occupational diseases.**"

National Ethics Advisory Committee

- **expressed reservations about the use of diagnostic tests, but accepted the introduction of genetic screening in the workplace:**

"the possible repercussions of a genetic predisposition to a disease or of a pre-symptomatic diagnosis can only be assessed in the framework of medical aptitude for a job, to be determined by the occupational physician alone."

But this fitness must be assessed **at the time of the examination and not as a function of future risks.**

- **The use of pre-symptomatic or probabilistic diagnostic tests should not be authorized. Specifically, as long as the disease has not actually developed, the employee is not unfit for work.**

- **Rare exception:** *when the probability of a disease associated simultaneously with a genetic predisposition and the workplace environment is very high and there is no possibility of eliminating or reducing the hazard by modifying the environment.*

“Science without conscience is but the ruin of the soul” Rabelais

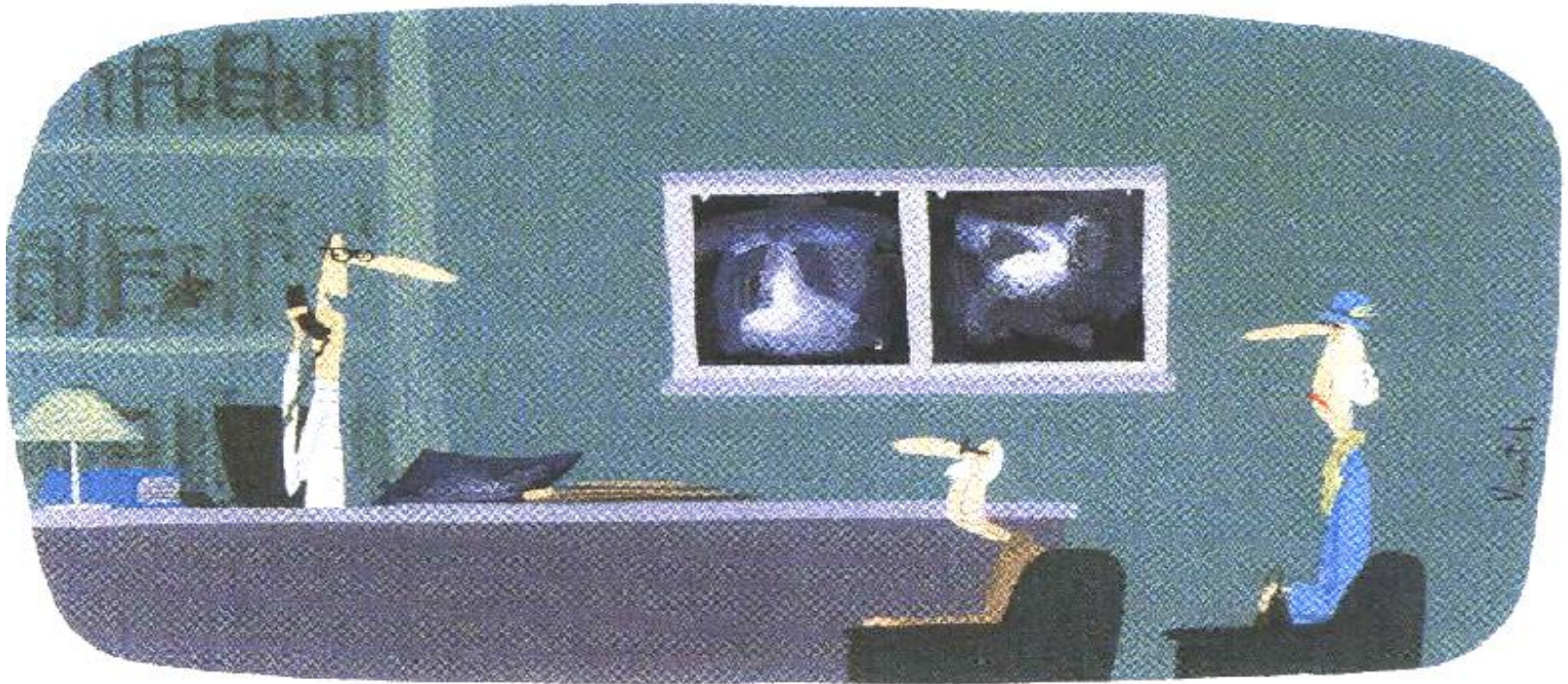


- These tests, in the guise of preventive health, may appear to be an instrument of selection **because their aim is not only diagnostic, to assess current unfitness, but also predictive. They are thus a source of numerous uncertainties while claiming to determine the future unfitness of individuals currently not ill.**

- Act No° 2002-303 of 4 March 2002, Title II, article 4 of the law related to patients' rights, bans all genetic discrimination in the civil, penal and labor codes:

"No one shall be discriminated against because of his or her genetic characteristics."

CONCLUSION



Darling, can I call you back later?
I'm in a meeting with a future widow and her husband.