Mutagenesis and Cancerogenesis. Anthropological Perspectives

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MUTATIONS

All mutations correspond to alterations of the nucleotide sequence of the DNA, they are of genic or chromosomic origin. Genic mutations correspond to little modifications of sequences, sometimes as short as only one modified base (as on the ß-globin of hemoglobine with a change of the 6th codon of the 146 codons, in the case of a sickle cell anaemia). The chromosomic mutations can result in more drastic alterations, such as deletions, duplications, inversions or translocations. For instance, a reciprocal trans-location between the chromosome 9 and 22 is observed in myelogene chronical leucaemia: the translocated chromosome 22 stimulates a gene leading to leucaemia, it is also called *Philadelphia chromo-some*.

These mutations are hereditary if they are present in the gametic cells, but they can also be somatic and linked to ageing problems or to cancers.

MUTAGENIC OR CANCEROGENIC SUBSTANCES

Substances or factors resulting in higher frequencies of mutations are called mutagenic. These same substances are very often at the same time cancerogenic : the cancerogenic substance (Tables 1 and 2) is indeed or directly mutagenic or transformed in a mutagenic substance after some metabolism. The classification of cancerogenes is a function of their effects and of the way they react directly or not with DNA. Carcinogens, which are linked to DNA, are potentially genotoxic mutagenes, others are indirectly mutagenes (such as aneugene or mitogene factors) (as hormones and inductors of proliferation of peroxisomes) (Aardema et al., 1988).

Ionising radiations but also radon (radioactive gas resulting of the fission of the ground uranium) are also mutagenic and cancerogenic : it is essentially X-radiations (often in medical use) and γ radiations which are highly energetic, β are less energetic and α even less (Table 3). The essential effects correspond to the liberation from water of free radicals (Fig. 1), which can modify the structure of the DNA bases and result indirectly in breaks of DNA strings. The UV radiation can also be genotoxic : the UV-C (<280 nm) are influencing directly DNA but are completely absorbed by the atmosphere, the UV-B (280-315 nm) are also biologically active and are for a large part filtered by the ozone layer (the depletion of stratospheric ozone increases the penetration of these UV-B).

Table1: Examples of relationship between cancer and carcinogenic factors

Cancer	*Examples of known carcinogenes*
Mouth	Tobacco, alcohol
Brain	Ionising radiations
Colon and rectum	Food low in fibres, rich in fat
Stomach	Tobacco, salting
Liver	Alcohol, virus of hepatitis
Leucaemia	Benzene, ionising radiations
Lymphoma	Some viruses
Melanoma of the skin	UV radiations
Pancreas	Tobacco
Lungs	Tobacco
Prostate	Testosterone
Breast	Oestrogene, food rich in fat
Bladder	Tobacco
Uterus	Oestrogene

Table 2: Factors and cancerogenic substances

Factor	*Substances*
Ionising radiations : X-rays, α, β, γ radiations	Tobacco (at least 40 substances individually cancerogenic such as benzo(a)pyrene, aromatic amines, aldehydes and nitrosamine)
UV radiations	Alcohol
	Asbestos
	Alkyling products: chloride of vinyl, mustard gaz
	Nitrate/nitrite (transformed in nitrosamines)
	Aflatoxine (of mushroom origin)
	Amino heterocyclic products (after pyrolysis)
	Safrole (of plant origin)
	Aromatic polycyclic hydrocarbure (after pyrolysis)
	Benzo(a)pyrene
	Arsenic
	Radon (responsible of 1/20 lung cancers)
	Cyclosporine

Table3: Doses of ionising radiations of the general population

Mean annual doses : 2.2 milliseverts/year
10% cosmic radiation
14% ground uranium
12% X-rays of medical origin
0.5% fall-out of nuceal explosions

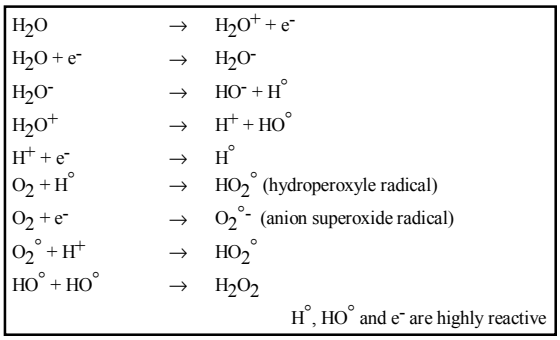


Fig. 1. Effects of ionising radiations, development of free radicals

Diverse methodologies of detection of mutagenic substances exist (table 4).

Different enzymatic systems allow to correct genic mutations as in the case of a bad link of DNA bases: these enzymes allow to verify the link of nucleotides during the replication (exonuclease), others verify it after the replication but before methylation, and still others during the whole life of the cells (reparation by excision). A mistake at gene level is about 10^{-6} but may reach 10^{-3} when the exonucleases are not functionning for example. In case of low levels of cancerogenes, the process of DNA reparation can be more efficient or the damaged cells can more easily be eliminated. By this way, one can get the impression that a threshold effect would exist in the influence of cancerogenic factors.

CANCERS

Cancer is a variability of disease where the cells escape from the mechanisms of control limiting normally their growth and their division. The cancer will develop through different steps, such as the initiation (mutations leading to a latent period), the promotion (the latence is expressed) and the progression (development of a tumor) (Fig. 2).

The cancer is surely a multifactorial disease but where the weight of genetic factors is far less negligible.

Cancer cells differ from normal cells, from which they are issued, by the loss of control of cell divisions : they divide in a more or less continuous way and then constitute tumors. These are or benign (being localised and with cells of morphology similar to the ones of the tissue of origin), or malign (the cells are dedifferentiated and do not have the morphology anymore of origin, they express the gene of telomerase and the telomeres are thus not reduced during each division, they can invade other tissues and thus create metastasis).

The cancer transformations are essentially of genetic origin by the presence of somatic mutations. These somatic mutations are as well chromosomic as genic, they can appear spontaneously or under influence of cancerogenic factors, such as ionising radiations, UV radiations, chemical substances of tobacco or of salting for instance.

Eventually, non cytotoxic products may be activated in electrophile kinds highly reactive with DNA, such as through the p-450 cytochrome system (fig. 3). The genes of this sytem are very numerous, varying between 60 and more than 200. In the example of the benzo(a)pyrene (Fig. 3), the risk of cancer increases through a polymorphism of the cytochrome enzyme (CYP1A1) producing more metabolites and/or the enzyme GSTM1 inducing less detoxification (Crews and Hanley, 1995).

ONCOGENES AND SUPPRESSORS

Two kind of genes are often mutated in numerous cancers, the proto-oncogenes and the tumoral suppressors. The proto-oncogenes have the capacity,

Table 4: Examples of tests for detection of mutagenic substances

Test	*Organism*	*Particularities*
Ames	Salmonella his^- (histidine negative)	Adding to the culture environment of liver extracts (containing cytochromes p450 oxydases). Calculation of back mutations (histidine free)
Muller-5 test	Fruit flies	Utilisation of organisms from which the genetics is well known.
Comet	Cells *in vivo* or *in vitro*	Breaks are visible through a more rapid migration of DNA.
Micronucleus	Mammalian cells *in vitro*/bone marrow *in vivo* or spermatide *in vivo*	Containing one or more fragments of chromosomes, induced by clastogenes or aneugenes..
FISH (Fluorescence *in situ* hybridisation)	Mammalian cells *in vitro*/ somatic or germinal cells *in vivo*	Possible influence of other cell processes.
Chromosomic aberration	Human cells (*in vivo* or *in vitro*)	By study of caryotypes.
Sister chromatide exchange (SCE)	Cells *in vitro* or *in vivo*	Linked to reparation of DNA.
Analysis of caryotypes	Mammalian cells *in vitro* or *in vivo*	More heavy and less sensible technique

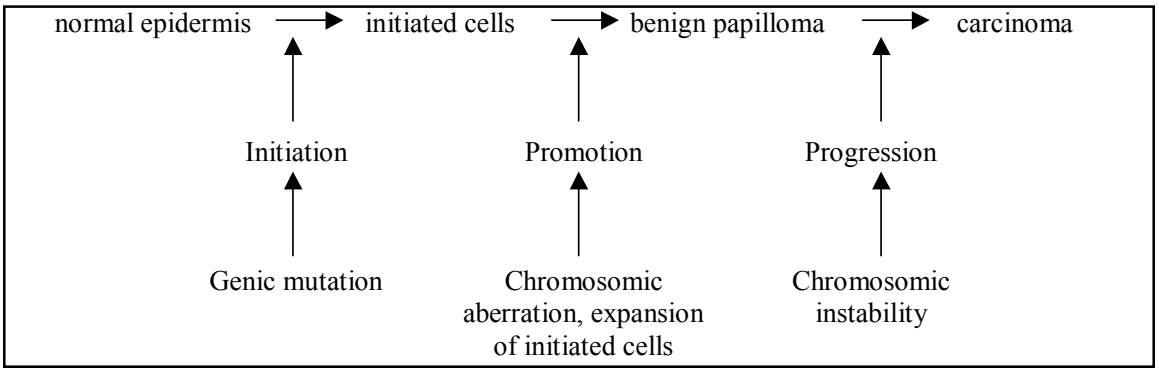


Fig. 2. Cell changes during the skin carcinogenesis

in different ways, to regulate the cell divisions (Table 5), after a mutation the divisions become uncontroled (Eylenbosch et al., 1991).

The mutations of proto-oncogenes can be of different kinds. A genic mutation can produce a new protein stimulating more actively cell growth. The mutation can also induce a multiplication of gene copies, the normal protein being in excess, or can also induce a change of position of the gene, linked to a new promotor the protein can again be produced in excess. More than 50 oncogenes are actually known: one of the well best knowns is the *ras* gene from which the mutation is present in 20% of human tumors and in 50% of colon cancers. The *ras* oncogene corresponds to a punctual mutation: in position 12 of the protein glycine is replaced by valine.

Different tumoral suppressors genes are known, their two alleles must be mutated to result in a cancer situation (Table 6). These genes control the processes of the cell cycle such as the genes p53 and Rb active during the G1 phase: they stop the cell in this phase. The mutations of the p53 gene found in tumors are not situated at random, they are the most often situated between the codons 130 and 290 (exons 5 to 9). In case of high numbered changes, p53 can activate other genes resulting in the cell apoptosis: the cell death is genetically programmed to avoid too deleterious effects.

Hereditary kinds of cancers can appear in families where a mutation of a suppressor gene is transmitted and where only one mutation of the other allele is sufficient to result in a cancer. The suppressor genes are implicated in cancers such as the retinoblastoma or in 9% of the women with a mutation of the BRCA1 and BRCA2 genes (chromosome 17) where 60% will develop a breast cancer before age 50 and 82% before age 70 (the frequencies of women with 2 normal genes are respectively 2% and 7%).

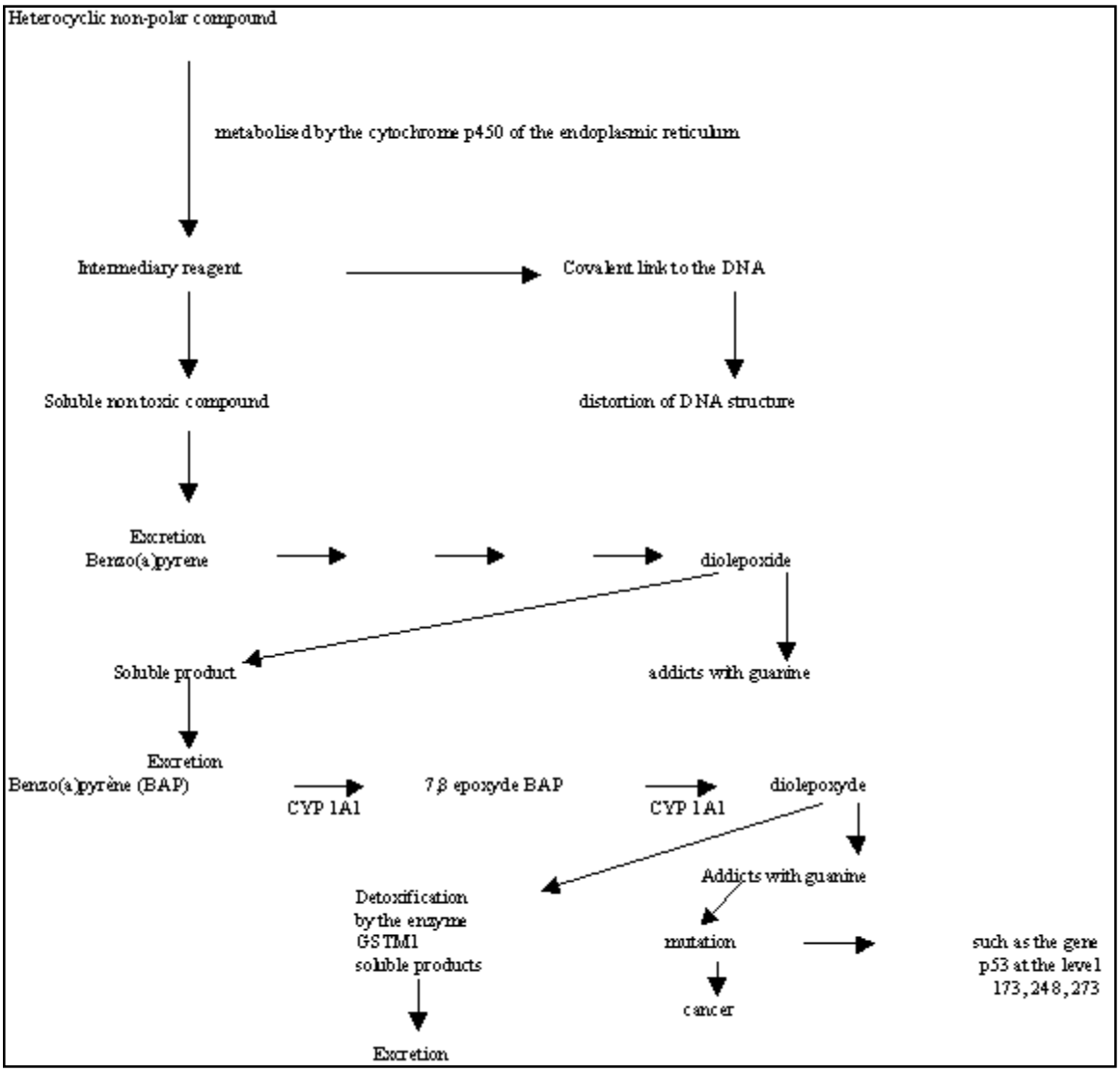
Even in the case of cancers of viral origin, these suppressor genes could have an influence. For instance, in the case of anogenital cancers due to the infection of papilloma virus, the genome of the virus is producing 2 proteins E6 and E7, which could link and inactivate respectively the p53 and Rb genes : when these 2 suppressor genes are inactive, the cell division can start.

Table 5 : Cell division and proto-oncogenes

Following the type of proto-oncogenes	
Normal effect	*After cancerogenic mutations*
Growth factors stimulating neighboring cellular division.	Overproduction of growth factors, auto-stimulation of division.
Growth factor receptors.	The link with growth factors seems no longer necessary.
Transduction signal: proteins transmitting external division stimulants.	Signal remains constantly active.
Factors of transcription activating genes implicated in division.	These factors are still linked to these gene promotors.
Apoptosis control (programmed cell death).	Cell death no longer occurs.

Table 6: Multiple process transforming the regular cell into a cancer cell : example of the coloncancer

Stages	*Effects*
↓ Normal cells of the colon	
Loss of suppressor gene of chromosome 5	↓ Polyp in the colon wall
↓	Precancerous benign tumor
↓ Activation of the oncogene of chromosome 12	↓ Growth of a benign adenoma (of class II)
↓ Loss of suppressor gene of chromosome 18	↓ Growth of a benign adenoma (of class III)
↓ Loss of suppressor gene of chromosome 17	↓ Development of a malign carcinoma
Other changes	Metastasis



CYP1A1 is located in 15q22-24 and shows at least 5 alleles

Fig. 3. Metabolism of non-polar aromatic polycyclic compounds by the cytochrome *p450* (CYP) system. Example of benzo(a)pyrene

A better knowledge of these genes can thus lead to the development of tests of genetical screening.

DIAGNOSIS

In the carcinogenic process, and its diagnosis, the measure of DNA addicts seems of importance ; they are linked to the electrophile reactivity and to chemical damages of DNA leading to mutations (Fig. 4) : this measure evaluates the internal dosis of cancerogenes and the potentiality of cancer development.

The epidemiologic studies may also help to identify the external causes of cancer. To identifiy a cancerogenic factor does not unfortunately eliminate it: the best example is tobacco smoking, which is responsible of at least 30% of cancer deaths, and is known for at least 30 years, but the society does not have the courage to forbid to smoke, at least in public.

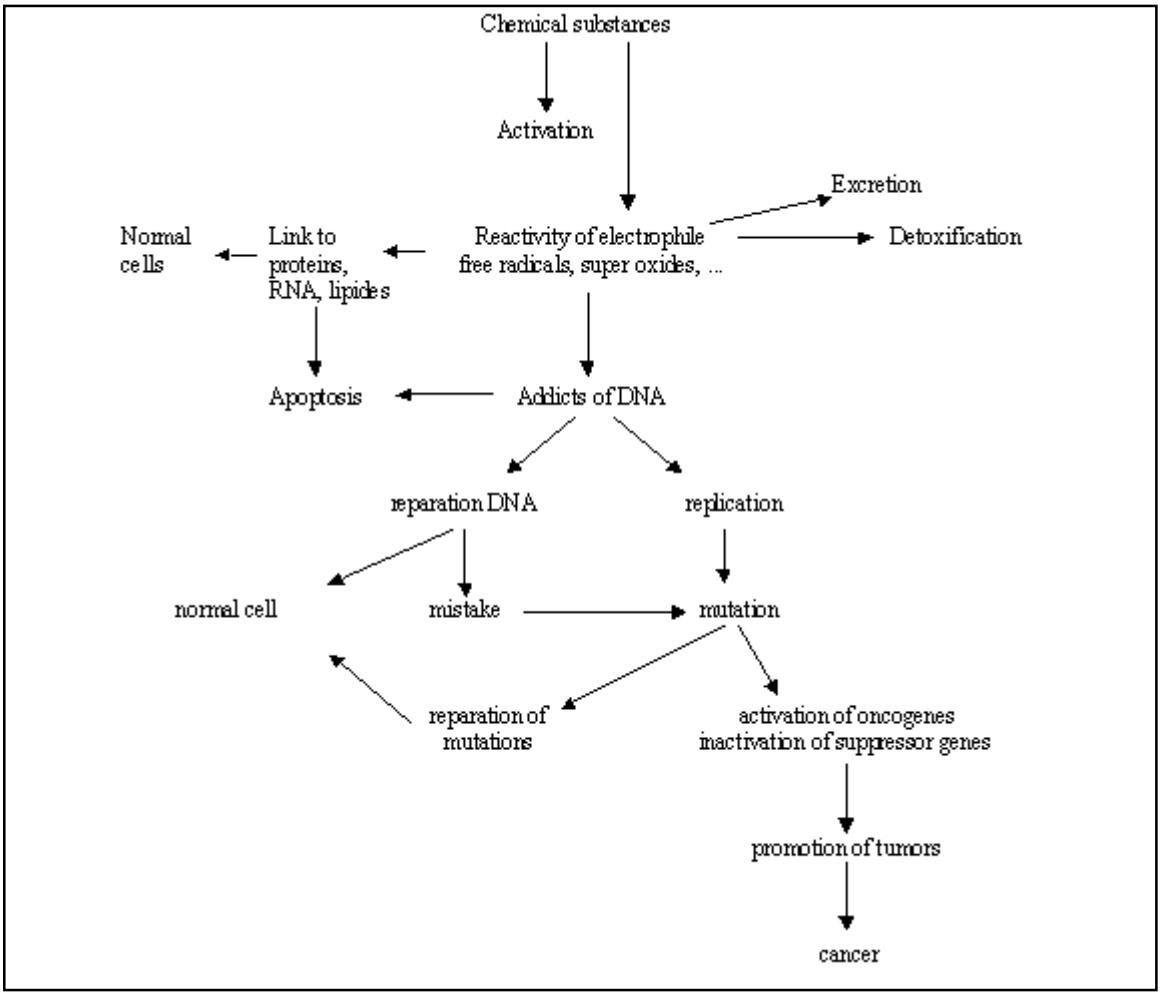


Fig. 4. DNA addicts and their biological consequences

ANTHROPOLOGICAL CONCLUSIONS

Our anthropological goal is naturally not therapeutic or even not diagnostic. It could be, however, the predictive tests because they are based on a genetical polymorphism: it is even becoming a truism to say that our capacity to predict exceeds largely the curative capacities.

These predictive tests imply, however, ethical problems which cannot keep us indifferent. Which are the limits of these tests applications ? Which is the safeguard of analysis anonymity? Can the informa-tion be required by the labour medicine? Are the insurance companies allowed to practice these tests? Is the genome of a person a private property, can it be selled? The genetical tests may participate to a better preventive medecine but may not become discriminatory. Individuals or populations may not be stigmatised or ostracised by their genes.

As for all multifactorial factors, an interindividual and interpopulational variability exists. These epidemiological data are of interest for anthropologists because they involve environmental but also genetical factors (Burdon, 1999).

It is interesting and encouraging to know that the control of exposure to xenobiotics of our diet and of our style of life can help to limit the risks. But, the genetical susceptibility exists as well as a poly mor-phism of proto-oncogenes, of tumoral suppressors and of enzymatic systems (theoretically detoxifying such as the p450 cytochromes but able to create DNA addicts).

KEY WORDS Mutation. Mutagenesis. Cancerogenesis. Cancer

ABSTRACT Epidemiological data on cancer are of anthro-pological interest, and are typical of mulfact-orial characteristics with a mixing of environmental and genetical influences. A genetical susceptibility exists: of in-terest is the polymorphism of proto-oncogenes, of tumoral suppressors, of enzymatic systems such as the cytochromes p450 (theoretically detoxifying but able to produce DNA addicts).

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