ABSTRACT
The concept of cancer “etiology” seems inadequate, at least in its classical use in the pathology of infectious, parasitic, nutrition, metabolic diseases. We consider the use of the terms carcinogenesis, cancer inducing factors or carcinogenic factors more adequate for what happens during tumor cell transformation, with the mention that the term carcinogenesis defines the initiation of a tumor, and oncogenesis its maintenance and subsequent evolution.

In conclusion, we believe that the use of the notion of risk factors is adequate in approaching the complex process of carcinogenesis.

The main carcinogenic factors can be grouped into:

1. primary determining factors;
2. secondary determining factors;
3. favoring factors.

KEY WORDS: radioleukemia, radiodermatitis, Albinism and Xeroderma pigmentosum.
INTRODUCTION

PHYSICAL FACTORS

Different types of non-ionizing and ionizing radiations are majorly involved in the mechanisms of carcinogenesis.

Non-ionizing radiations are electromagnetic, with low penetration, and present a real danger for eyes and skin. This group includes ultraviolet radiation, light radiation and infrared radiation, all having the sun as the main source.

Ultraviolet B rays are mutagenic and carcinogenic, but they have a weak penetrability of only 10%, being stopped by the horny layer. They are absorbed by the ozone layer. Ultraviolet A rays penetrate the dermis easily.

Albinism and Xeroderma pigmentosum are hereditary factors predisposing to actinic cancer. Experimental actinic cancers are sarcoma like cancers. The main spontaneous actinic cancers in domestic animals are: vulvar melanoma in Angora goats; conjunctival squamous cell carcinoma in Hereford and Norman cattle; squamous cell carcinoma in Scottish Shepherds; squamous cell carcinoma of the external ear in white cats; squamous cell carcinoma of the external ear in sheep.

Directly ionizing radiations are electrically charged particles: negative charge, electrons, such as beta rays; positive charge, alpha particles.

Indirectly ionizing radiations are particles without electric charges: photons, X rays and Gamma rays.

The biological action of the ionizing rays depends on numerous factors: doses distributed in time add their effects, acting through summation; they can act by a single dose; their action is influenced by the presence or absence of radiosensitizing substances, such as oxygen, and radioprotective substances; the species can be more sensitive or on the contrary, resistant. For each species the following will be taken into account: the water and oxygen content; the mitotic index and the degree of tissue differentiation.

Regarding the biological action, the major impact is at the level of the cell nucleus, chromosomes (ruptures, deletions, translocations) and DNA (thymine peroxidation, rupture of a phosphorylated bond at the level of a chain and breakage of one or two filaments). The cytoplasm is another target site, causing: arrest of metabolism after the destruction of enzymatic molecules, alteration of mitochondrial and lysosomal membranes, with the release of the enzymatic content.

These biological actions result in either the death or the survival of the cell as carrier of a mutation. In human pathology, radioleukemia and radiodermitis that induce squamous cell carcinomas in radiologists are well known, as well as infant leukemia following fetal radiation, thyroid cancer after cervical radiation, etc.

Experimental local radiation in rats causes radiodermitis evolving into sarcomas; thyroid cancer and hypophyseal tumors.

Cancers induced by radiation are characterized by late onset, after 10 or more years, risk persisting over a period longer than 30 years.

Repeated low intensity traumas can determine metaplastic, dysplastic changes, and even tumor proliferation. The involvement of traumas in the development of tumors should be regarded with circumspection, since exophytic tumors are submitted to the action of traumatic factors that cause erosions and ulcers.
Osteomas occurring at the level of bones on which repeated traumas are exerted is well known in animals.

CHEMICAL FACTORS

The first observation in the natural history of carcinogenesis concerning the intervention of a substance in the appearance of a tumor belongs to Sir PERCIVAL POTT, from 1775. This London doctor understands that there is a relation between soot and the appearance of scrotal cancer in chimney-sweeps. Other observations have been subsequently reported. Thus, in 1874, VOLKSMANN remarks the high incidence of skin cancer in tar workers. REHN (1895) describes bladder cancer in workers who come in contact with aromatic amines. Experimentally, YAMAGIWA and ICHIKAWA (1915) succeed in inducing ear cancer in rabbits, by repeated tar applications.

Clinical and epidemiological observations have demonstrated the increased frequency of a certain cancer type, in a certain geographical area, within a group or profession, correlated with the presence of toxic chemical agents. These findings have led to the notion of carcinogenic substance.

At present, researchers aim to detect the relations existing between the structure of a substance and the carcinogenic effect, to identify ultimate metabolism before biodegradation, air and food pollution, etc.

According to MAGNOL and ACHACHE (1983), the main carcinogenic substances can be classified as follows: mineral substances, organic substances and mixed substances (tobacco, food carcinogens, etc.).

Chemical carcinogens act either directly, causing mutations, or indirectly, reactivating repressed carcinogens.

Depending on the mechanism of action of the chemical substance, WEISBURGER (1976) distinguishes three classes of chemical carcinogens:

1). Direct action or ultimate carcinogens, whose structure confers them the capacity to induce cancer without a previous metabolic activation in the host organism. This category includes nitrosamines, epoxides, ethylenimines and β-propiolactone.

2). Procarcinogens, group that includes the majority of chemical carcinogens that become active after a previous metabolic activation to ultimate carcinogens. Known procarcinogens: aminozoic colorants, aromatic hydrocarbons, aflatoxins, aromatic amines and urethane.

3). Co-carcinogens, which are chemical substances that cannot induce cancer when they are administered alone, but can enhance the carcinogenic effect of other substances. In general, co-carcinogens act as promoters in tissues in which the initiation stage has appeared. Through the reticulo-endoplasmic system, the detoxification of the organism from foreign substances usually occurs by hydrolysis, reduction, conjugation and oxidation, with renal elimination.

Chemical carcinogenic substances are first activated through the hepatic microsomal system, then they bind in a covalent form to the macromolecules (DNA, RNA, proteins) from the target organs.

MINERAL CHEMICAL SUBSTANCES

Based on epidemiological data and clinical observations, mineral chemical substances have been identified to potentially induce tumor growth.

Arsenic induces hoof cancer in cattle and sheep grazing in the proximity of plants that
use arsenic. Skin and lung cancer occurs in arsenic workers.

**Asbestos** induces pulmonary and pleural mesotheliomas in miners and industrial workers who work with asbestos, as well as in animals from the proximity of mines.

Other mineral substances that can induce cancer are reported: **chrome** induces pulmonary tumors; **nickel salts** induce pulmonary and sinus tumors; **cadmium** induces prostate tumors, and the list is not exhaustive.

**ORGANIC SUBSTANCES**

These can be carcinogenic. **The group of aromatic substances** includes pitcoal tar, based on anthracene and phenantrene nuclei, which induces skin and cervical cancer and can have similar actions on the lungs, ovaries, etc.

The main aromatic hydrocarbons with carcinogenic action are: 7–12-dimethyl benzanthracene, which is extremely active, inducing skin cancer in the mouse; 3–4-benzopyrene, a major air pollutant (industrial smoke, cigarette smoke); 3-methylcolanthe, etc.

Among amines, the following products are known: 2-naphthylamine that induces bladder cancer in humans and dogs; 2-acetyl aminofluorene, which develops hepatic and bladder cancer.

**Azoic colorants** induce hepatic tumors.

**The aliphatic series** is represented by: amines (nitrosamines); alkylation agents and plastic packages. In all cases, with variable doses and exposure times, these have been experimentally demonstrated to have carcinogenic properties. Due to their extremely high number of compounds, their distribution in all environments (soil, water, air) and foods, as well as to their high carcinogenesis potential, nitrosamines have attracted the attention of researchers. Nitroso compounds are active in all species, having a specific action on the liver, respiratory system and kidneys.

“Diseases are caused by what we put in our mouth, and troubles by what comes out of our mouth” - Chinese proverb

**BIOLOGICAL FACTORS**

Numerous carcinogenic substances, either natural compounds or pollutants, are found in human and animal food. Over 80% of carcinogenic substances are found in the environment and are taken by living beings with air, water and food.

There are epidemiological data that prove the role of dietary factors in the etiology of human and animal cancers. An increased number of natural carcinogens are found in human and animal food, either as natural components or contaminants. Natural carcinogens have been identified in plants, microorganisms and animals.

**CARCINOGENS IN PLANTS**

By reviewing an impressive number of plant substances with carcinogenic action, LAI and WOO (1987) conclude that these are widely distributed in plants. Carcinogenic substances are present in ferns (*Pteridophyta*), in the more evolved coniferous species (*Gymnospermae*), as well as in the most phylogenetically advanced, superior plants (*Angiospermae*).

The majority of plant carcinogens have an activity that varies from weak to moderate. They are widely distributed in plants, including a large variety of structural types: pyrrolizidine and other heterocyclic alkaloids,
alkenylbenzene compounds, furocoumarins, etc.

**Bracken fern**, *Pteridium aquilinum*, which grows in temperate areas, has been proved to play a role in the onset of bladder, intestinal and other cancers, in some herbivorous species. Humans can be indirectly exposed by the consumption of milk, meat and secondary products from animals feeding on ferns. The high prevalence of human cancer with esophageal and gastric location in certain regions from Japan and North Wales has been correlated with the exposure to toxins of the bracken fern. Relative risk increases in subjects who consume hot seed tea and who smoke cigarettes daily.

The toxins identified in this fern, suspected or tested for carcinogenicity, are: shikimic acid, pterolactam, petrosius and pterosides, ptaquiloside, glycosides, kaempferol and tannins. The main carcinogenic compound seems to be **ptaquiloside**, which induces mammary tumors, intestinal tumors and hematuria in rats. Other chemical substances from the fern (shikimic acid, quercetin, rutin and tannins) have a synergic role in fern carcinogenesis.

Epidemiological observations have proved that other plants (Cyclamen) can induce cirrhosis and/or liver cancer.

**Pyrrolizidine alkaloids** are the first plant products proved to be carcinogenic. In 1950, COOK et al. succeeded in inducing hematomas in rats, by the administration of alkaloid fractions extracted from *Senecio jacobea*. Later, other plant extracts containing pyrrolizidine alkaloids were experimented, and their carcinogenic capacity was demonstrated. In general, few long-term experiments with hepatotoxic pyrrolizidine alkaloids have been performed to demonstrate their carcinogenic action. Experiments have proved that all hepatotoxic alkaloids, as well as their metabolites, induce liver carcinomas in the rat, causing tumors in other organs as well. The cited authors mention among carcinogenic pyrrolezidine alkaloids: monocrotaline, dehydromonocrotaline, lasiocarpine, heliotridine, dehydro-heliotridine, retrorsine, etc.

The implication of pyrrolyzidine alkaloids in human carcinogenesis has been observed by the study of consumption episodes of plants containing these hepatotoxic alkaloids. The literature mentions such episodes in which human populations have consumed plants, seeds or food products contaminated with hepatotoxic alkaloids. Pyrrolyzidine alkaloids were identified in cow milk, as well as in the honey of bees from a pasture with a flora rich in *Senecio jacobea* and *Echium plantagineum*. In the Bantu population from South Africa, a high incidence of liver cancer was found, correlated with the use of *Senecio sp.* plants, for medicinal and nutrition purposes. The same effect was noted in Bedouins from Kuwait, who used the *Heliotropium ramosissimum* plant for various purposes (SCHOENTAL, 1982). The mentioned observations, and many others, do not clarify the direct relation between pyrrolyzidine alkaloids and their carcinogenic action.

In plants, in addition to alkaloid carcinogens, other carcinogenic or co-carcinogenic factors tested on experimental animals have been identified. Such factors are: reserpine, sanguinarine, nicotine, arecoline, acronycine and caffeine.

**Reserpine**, widely used in hypotensive medication, has been proved to be carcinogenic in mice and rats, inducing hepatomas, lymphosarcomas, carcinomas of the adrenal glands, mammary and seminal vesicles. The possible association of reserpine
use with the development of mammary carcinoma in women has been long debated. Epidemiological studies have not clarified this issue, and it has been concluded that a positive association would be possible, but with a low risk.

Sanguinarine is present in *Argemone mexicana* and in the plants from the *Papaveraceae* family, which are distributed in the tropical and temperate regions of the world. The populations from these areas consume contaminated products (oil, eggs, milk, liver, etc.), directly or indirectly, through animals feeding on plants or seeds that contain sanguinarine. HAKIM's observations demonstrate as early as 1968\(^2\) a direct correlation between the geographical distribution of plants containing sanguinarine and the increased incidence of esophageal and gastric cancer in people living in these areas. The same author shows a connection between opium smoking, which contains sanguinarine, and the high incidence of esophageal cancer in populations from China and Philippine.

Nicotine is the alkaloid to which modern man is the most exposed.Nicotine is contained by *Nicotiana tabacum* and *Duboisia hopwoodi*, the direct relation between pulmonary cancer and smoking being demonstrated without any doubt. The main carcinogenic or cocarcinogenic agents from cigarette smoke are polycyclic aromatic hydrocarbons; it is possible that nicotine plays the role of a co-carcinogen or promoter or both, since neoplasms develop in the liver and intestine of rats that receive nicotine or its main metabolite, cotinine\(^26\), in food. The World Health Organization estimated in 1999 that in 2020 tobacco would be the main cause of mortality, accounting for the death of 1/3 of all male Chinese who are today 30 years old.

Other derivatives of nicotine, the nitrosamines: N-nitrosonornicotine; 4(methyl nitrosamine)-(3pyridyl)-l-butanone, have carcinogenic properties in rodents.

In South-East Asia, the habit of chewing tobacco or betel nut (*Areca catechu* and *Piper betle*) coincides with an extremely high incidence of oral, pharyngeal and esophageal cancer. The main alkaloid of these plants is arecoline.

Caffeine is used in medicine especially as an analgesic and stimulant. The consumption of tea, coffee and other beverages has not been proved to be carcinogenic. The experiments performed on mice and rats receiving caffeine in food or water over a period of 2 years have demonstrated an insignificant increase in tumor incidence. Other experiments support the induction of carcinogenesis by caffeine, with the development of microadenomas, papillary (sinusoidal) macroadenomas, diffuse macroadenomas and pituitary gland hyperplasia. Subsequent studies demonstrate a significant increase in the incidence of mammary carcinomas in mice, after caffeine administration.

Epidemiological studies bring to the foreground the correlation between coffee consumption and the incidence of leukemia, pancreatic, prostate and ovarian carcinomas, but also intestinal, laryngeal, pulmonary and mammary carcinomas\(^2\).

Acronycine is a derivative obtained from the ashes of *Acronychia baierii* bark, being experimented as a possible anticancer drug. This alkaloid has proved to be carcinogenic in rats, inducing mammary tumors, osteosarcomas and sarcomas or other peritoneal tumors.

Safrole, whose carcinogenic action was detected in 1960–1961, after it had been used
for years as a flavoring agent for beverages, has a moderately hepatocarcinogenic action on mice.

**Alkenylbenzene compounds** are also used as food additives in pharmaceutical preparations. These compounds are found in plants and spices (carrots, bananas, parsley, black pepper, sassafras, clove, anise). Alkenylbenzene compounds induce cancer with various locations in small rodents.

**Essential oils**, extracted by distillation or partial solvent extraction from seeds, roots, rhizomes and bark, contain alkenylbenzene compounds. The use of safrole and isosafrole as aromatic substances for beer has been forbidden in USA. Oil extracts from different plants such as acorus and tarragon, used as flavoring agents in liquor or food, have been forbidden. Tannin from different tea varieties has been proved to have carcinogenic properties.

In conclusion, before being recommended for therapeutic purposes, the various plant extracts should be rigorously and scientifically studied, including from the point of view of possible carcinogenic actions.

**Psoralen and other furocoumarin products** are present in the fruits, seeds, leaves and roots of plants from the Umbelliferae, Rutaceae, Leguminosae, Moraceae and Orchidaceae families. Furocoumarin compounds are principles with moderately carcinogenic action.

**Carcinogenic plant phenols**

Some phenolic compounds from food plants are inhibitors of tumor inducers, while a number of plant phenols have a moderately carcinogenic action. The latter category includes: tannins, quercetin, rutin, capasicin, rotenone and gossypol. Tannins, which belong to a group of polyphenolic compounds, have been suspected of having carcinogenic properties, after their excessive use in the treatment of burn induced wounds. These suspicions have been verified by the subcutaneous injection of tannic acid in experimental animals, which has determined the appearance of hepatic tumors. The subcutaneously injected tannin fraction from tea, *Camellia sinensis*, is carcinogenic in rodents.

Tannic acid is used in various finishing procedures of some foods as a clarifying substance, in the refining and flavoring of beverages or pastry products. The condensation water from tannins is widely distributed in human foods and especially in cider, cocoa, tea and red wine (sometimes with a content of over 1g per liter); tannin is also present in some fruits and plants such as spinach, plums and bananas. Hydrolyzable tannins are less frequent in human foods.

Epidemiological studies performed by MORTON (1986) have demonstrated a close connection between the high incidence of esophageal cancer in different geographic areas and the consumption of tea made of tannin-rich plants and/or the use of traditional medicine. The majority of these drugs, plant beverages, contain carcinogenic tannins, while others contain carcinogens of the safrole group.

**Flavonoids** are present in many plants and fruits, having beneficial biochemical and pharmacological effects on humans. These products have been suspected of having carcinogenic effects. Thus, in 1980, PAMUKU demonstrated the carcinogenic action of quercetin and rutin, which induce intestinal, bladder and/or liver neoplasms, in the rat. Numerous plant foods contain quercetin, rutin...
and other flavonoids in high concentrations, especially in green leaves and fruit skin.

**Capsaicin** is the main spicy substance from the fruit of different *Capsicum* species, such as hot pepper or red pepper. The carcinogenic action of capsaicin has been experimentally demonstrated in mice, which have developed duodenal adenocarcinomas.

**Gossypol**, another polyphenolic product, is a major toxic agent from cotton, *Gossypium hirsutum*. Cotton oil is used in Egyptian cuisine; applied on skin, it can be a neoplasm initiator or promoter.

Plants of the *Aristolochia* genus contain *aristolochic acid*, and extracts from these plants are used in contemporary medicine in arthritis, gout, rheumatism and purulent wounds. Experimental studies have demonstrated that aristolochic acid stimulates defense mechanisms, having antiviral, antibacterial and antimycotic properties. In rats, after a 3 months treatment, it has induced gastric, renal and bladder carcinoma.

**MYCOTIC TOXINS**

Aflatoxins are produced by different stems of the *Aspergillus flavus* and *Aspergillus parasiticum* fungi. The aflatoxin precursors - *sterigmatocystin* and *versicolorin A* - can be additionally found in certain stems such as *Aspergillus versicolor*, *Aspergillus nidulans* and *Aspergillus sydowi*. The exposure of man to aflatoxins occurs especially as a result of the consumption of foods contaminated with these moulds. The farming products which are the most susceptible to aflatoxin contamination are: corn, peanuts, copra (coconut oil) and cotton seeds. Wheat, rice, sorghum and oats, as well as other small seeds, can be affected as a result of environmental conditions favoring the development of moulds. The main aflatoxins identified in contaminated samples are: AFB1, AFG1 and, to a smaller extent: AFM1, AFB2 and AFG2.

Peanuts used for oil extraction can contain AFB1 in variable amounts, from several micrograms to over 1 mg/kg. A similar situation is found in cotton seeds. In addition to food plants and products resulting from these, another source of human exposure to aflatoxins is the milk or meat of animals receiving food contaminated with mycetes that produce aflatoxins.3

For the first time, the Romanian researchers CONSTANTĂ ADAMESTEAU, JIDUC and COTIGĂ (1959) have reported the occurrence of biliary adenomas in ducklings feeding on moldy food, with Aspergillus sp.

The interest in aflatoxin carcinogenesis studies appeared in 1960, as a result of the outbreak of the "turkey X disease" in the poultry farms from the United Kingdom and Kenya. The peanuts used as protein supplements in the food of poultry proved to be associated with the disease, and the toxic agents from peanuts were identified as aflatoxins (CARNAGHAN, 1965). The "toxic" peanut flour induces liver neoplasms and pulmonary metastases in the rats whose ration contains 20% of this flour.5

The experiments performed on different animal species (fish, birds and mammals) have shown that AFB1 is carcinogenic. The carcinogenetic potential of aflatoxins has been determined to be in decreasing order: AFB1, AFG1, AFB2 and AFG2.

Epidemiological studies have supported the association between aflatoxin consumption and liver cancer. These studies provide data revealing an etiological or contributive role of aflatoxins in the induction of liver cancer in humans.
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Tolerance limits for aflatoxins in human food range between 0 and 50 micrograms/kg (STOLOFF, 1977²).

The carcinogenicity of sterigmatocystin has been demonstrated in the mouse, the rat and the rainbow trout. Versicolorin A, a biosynthetic precursor of sterigmatocystin, has a weak carcinogenic action, inducing hepatomas.

Toxins produced by the Penicillium genus

The prolonged feeding of mice with moldy food induces neoplasms. Thus, mice feeding on rice parasitized with Penicillium viridicatum, a fungus that induces ochratoxin A, citrinin, penicillic acid and griseofulvin, have presented pulmonary neoplasms, incidence being by 75% higher than in controls. Similar results have been obtained in mice fed on rice infested with Penicillium islandicum, which elaborates luteoskyrin, cyclochlorotine and islanditoxin, toxins that induce liver neoplasms.

Experiments have demonstrated without any doubt the carcinogenic action of the following mycotoxins: ochratoxin A, griseofulvin, luteoskyrin and cyclochlorotine (MIYAKE and SAITO, 1965; ENDOMOTO, 1978²).

Some studies indicate the carcinogenic potential of citrin, PR toxin and rugulosin. The subcutaneous injection of patulin, penicillic acid and G penicillin in rats has revealed tumorigenic properties.

Mycotoxins also have carcinogenic effects in the organs or tissues on which they have a toxic action. Thus, the hepatotoxins: luteoskyrin, rugulosin, cyclochlorotine and griseofulvin induce liver neoplasms, while nephrotoxic citrinin is carcinogenic for kidneys. It should be mentioned that mycotoxins from the penicillium group can be carcinogenic for other tissues, such as the thyroid, the uterus, etc.

Fungi of the Penicillium genus, as well as of the Aspergillus genus, frequently develop in human and animal food stored under inadequate conditions.

Ochratoxin A has been detected in corn, wheat, rye, oats and barley mixtures, beans and peanuts. An increased incidence of nephropathies has been found in swine fed on moldy food in which ochratoxin has been identified⁶.

Citrinin has been detected in meat, rice, oats and cereal mixtures (SCOTT, 1977²). The same author mentions the presence of citrinin in rotten apples. One of the citrinin-producing fungi, Penicillium citrinum, has been isolated from Japanese "yellow rice".

Patulin is found in rotten apples and in derived products. The patulin concentration in the cider obtained from rotten apples can be of up to 45 mg/l (SCOTT, 1977²).

Penicillic acid has been identified in moldy corn and moldy animal feed, and also in moldy dry beans and tobacco.

In highly moldy rice ("yellow rice"), carcinogenic toxins are found, such as: luteoskyrin, rugulosin, cyclochlorotine, and islanditoxin, also known as "yellow rice toxins". Luteoskyrin is carcinogenic for rats, with a possible implication in human liver cancer¹⁴. Epidemiological studies have established that in Asia there is a direct relation between liver diseases, including cancer, and the consumption of rice contaminated with these carcinogenic toxins (WOGAN, 1969²).

Fusariotoxins, such as: T-2 toxin, fusarenone X, and zearalenone are produced by a great number of Fusarium sp., which infest farming
products (corn, wheat, barley, oats, straws and other animal feeds).

Sporadic outbreaks of mycotoxicoses, in humans and animals, due to Fusarium sp. infestations have been reported all over the world (BUSBY and WOGAN, 198; SCHOENTAL, 1984 2).

MUSHROOM TOXINS
Agaricus bisporus is the most common eatable culture mushroom. This mushroom contains agaritine, whose n-acetylate derivative causes a high incidence of pulmonary and blood vessel tumors, in rats. Other derivatives, administered subcutaneously in rats, induce cutaneous and subcutaneous tumors, and following oral instillation, gastric tumors25.

Wild mushroom extracts have proved to be carcinogenic for mice, which is why it has been recommended that half-wild brain mushrooms, Gyromitra esculenta, should no longer be consumed.

STREPTOMYCES TOXINS
The antibiotics produced from Streptomyces sp. are used in cancer therapy. Thus, actinomycin D, adriamycin, daunomycin C, sarkomycin, streptozotocin, azaserine and bleomycin repress tumor growth by selective toxicity to various tumors. Experimental and epidemiological studies have demonstrated that agents which inhibit the growth of preexisting tumors induce in their turn neoplasms when administered for a long time period.

This dichotomy is known as "Haddow's paradox"10. An increased number of antibiotics have proved to be carcinogenic in mice and/or rats. Carcinostatic antibiotics produced by Streptomyces sp. contain alkylating and/or intercalary fractions in the DNA, which makes them potentially carcinogenic. Primary tumors secondary to antibiotic administration are usually sarcomas, leukemia and other neoplasms of the hematopoietic system. It should be mentioned that patients were undergoing radiotherapy and other chemotherapeutic drug treatments.

Streptozotocin is considered to be carcinogenic for a number of animal species, which is why the International Agency for Research on Cancer has considered it a human carcinogen, in spite of the lack of epidemiological data.

ANIMAL CARCINOGENS
Cantharidin is the active principle of the gross drug called cantharides from Cantharis vesicatoria, Myleabris cichorii and other insects from the Meloidae,

Omeridae and Staphilinidae families, having rubefacient and vesicant effects on the skin and mucosae.

In nude mice, papillomas, squamous cell carcinomas, reticular carcinomas and/or malignant lymphomas have been induced by skin painting.

Cantharidin is a weak but complete carcinogen for the skin and the reticuloendothelial system of the mouse; it promotes skin tumorigenesis in mice, which is initiated by other carcinogens.

Quinones (1,4-benzoquinone and its alkyl derivatives), produced by insects from the Tenebrionidae and Opilionidae families, induce skin tumors and pulmonary neoplasms in mice, by subcutaneous injection, by inhalation, respectively.

Certain parasites, especially trematodes, are suspected of having a carcinogenic role in parasitized humans and animals. This is associated with the high prevalence of
gallbladder, liver cancer and other neoplasms, in the geographic areas where schistosomiasis is endemic. The carcinogenesis mechanism is not elucidated in this case, since the involvement of schistosoma toxins has not been experimentally verified. Experimental data have demonstrated the presence in the liver, serum or urine of animals with schistosomas, of high enzymatic levels, which can transform procarcinogens or promutagens into reactive metabolic products in certain host organs.

The parasites proved to be involved in tumor proliferations and mentioned by the literature are Schistosoma haematobium, which induces bladder cancer in humans, and Spirocerca lupi, which induces esophageal cancer in the canine species. In rats, the Gyngyloma neoplasticum nematode can cause under certain conditions gastric and tongue cancer. These parasites seem to induce tumors in both man and animals, by their irritating and less toxic action. Parasites cause local irritations, fibrous reactions, metaplasias, and finally, malignant changes.

ONCOGENIC VIRUSES

Causal virus-tumor relationships were established as early as the beginning of the century. In 1903, BORREL advanced the bold, even bizarre hypothesis for that time, of the infectious nature of certain cancers.

ELLERMANN and BANG (1908) succeeded in transmitting avian leukosis by acellular infiltrate. By the same method, of the acellular infiltrate, in 1911, ROUS and JONES transmitted the chicken muscle sarcoma, known today as the Rous sarcoma.

In 1936, BITTNER discovered that a “milk factor” is responsible for the mammary adenocarcinoma of the mouse. The murine leukemia virus (Mu.L.V.) was discovered in 1951 by GROSS, and HARVEY and MOLONEY isolated in 1964 the virus responsible for murine sarcomas (Mu.S.V). In the same year, 1964, the feline leukosis virus (Fe.L.V.) was identified by JARRETT, and in child lymphoma cell cultures, the Epstein-Barr virus (E.B.V) was identified.

In 1969, THEILEN and SNYDER discovered the feline sarcoma virus (Fe.S.V), and MILLER isolated the bovine leukemia virus (B.L.V). One year later, TEMIN and BALTIMORE discovered the RNA-dependent reverse transcriptase or DNA-polymerase. The data accumulated have contributed to HUEBNER’s theory of viral oncogenesis, and BISHOP has the merit to have enlarged the notion of oncogene. In 1978, FERS and WEISSMAN published simultaneously the first genetic map of an oncogenic virus. COLLETT and ERIKSON (1978) identified the transformed proteins encoded by the viral Oncogene.

Viruses are able to induce tumors in animals, but there is no specific virus that is alone the cause of all cancers. The great majority of cancers are not of viral origin. Oncogenic viruses behave as either simple infectious viruses – multiplying and destroying cells – or they do not multiply in cells, but change the biochemical, morphological, physiological characteristics of cells.

Both DNA and RNA viruses transform cells, their genes are incorporated, integrated in the genes of the host cell. In 1970, TEMIN and BALTIMORE proved concomitantly that carcinogenic viruses that contain RNA possess an enzyme, reverse transcriptase, which allows RNA replication in the DNA. This DNA replica can subsequently integrate in the DNA of the host cell.
A protein coded by a cancer gene of a virus will fix to a certain locus of the host cell DNA, which can result in the activation or inhibition of a gene group that is responsible for the cell transforming character.

The location on the cell membrane of the transformed proteins can explain cellular changes, by various mechanisms. Thus, a protein fixed on a membrane can modify the ion exchange between the cells and the environment, which can stimulate DNA synthesis, phenomenon that precedes cell division.

Cancer genes and the transformed proteins of different carcinogenic viruses can have common characters. Virus cancer genes have been proved to be genes of cellular origin, present in the genetic patrimony of the host-cell in a normal state.

Endogenous sarc genes are cancer genes, and the viral SRC gene is nothing else but the cellular sarc gene that the virus has incorporated when it has separated by excision from the genes of the infected cell, phenomenon known as transduction.

Cancer may appear by the introduction of a virus in a cell, the virus will cause the increase of the transformed protein amount, changing the cellular status by a gene dosage effect. Thus, the mouse mammary tumor virus (MMTV) is transmitted by spermatozooids and ovules, but hormonal and/or genetic factors also act in addition to the virus. So, the virus alone is not sufficient to determine a tumor cause, which is expressed by the term co-carcinogenesis. Viral co-carcinogenesis is usually caused by the activation of cell cancer genes, this activation being the consequence of the passage of cell genes under the control of a viral initiator.

The mechanisms of viral oncogenesis recognize two types: the cell-deoxyvirus (DNA virus) interaction and the cell-ribovirus (RNA virus) interaction.

1. The cell-deoxyvirus (DNA virus) interaction is carried out by the adhesion of the deoxyvirus to the plasma membrane, which penetrates the cytoplasm, then the nucleus, and finally dictates the future evolution of the cell, towards either lysis or transformation. After the virus has penetrated the cytoplasm, it disappears – the eclipse phase. It has been proved by various techniques, such as cellular and molecular hybridization, that the viral core persists in the nucleus of the infected cell. In cellular hybridization, in the eclipse phase, the infected cell merges with an uninfected cell, able to produce the virus – the permissive phase, representing a heterokaryon that provides viral particles.

By cell hybridization, if the viral genome is fixed to an isolated mRNA starting with the cytoplasm of the infected cell that is marked with tritiated uridine, it has been demonstrated that this mRNA is virus inducing and the viral genoma assembly is integrated in the cell genome.

After the integration of the viral core into the cell nucleus, there are two possibilities: the lytic cycle and the cell transformation cycle.

During the lytic cycle, the virus is replicated, then the lysis of the host cell occurs, and homologous cells become permissive, i.e. they permit replication. In the case of the Marek disease virus, for example, the homologous cells of the fowl are permissive. The lytic cycle takes place in the feather follicles and allows the development and multiplication of the virus.

After the feather loss of the infected fowl, the virus is dispersed horizontally by respiratory and digestive route.
The transformation cycle occurs in heterologous cells, in which cell transformation is initiated without the replication of non-permissive cells.

2. The cell-ribovirus (RNA virus) interaction.
During a first phase, the virus adheres to the plasma membrane, then penetrates the cytoplasm and the nucleus, and finally conditions the parasitized cell for cellular transformation or viral production.

During the infection stage, the cell manifests no particular change, neither transformation nor virus production. Proviral DNA, integrated in the cellular genome, is duplicated with the cell and transmits vertically the genetic information of postmitotic cells. The transformed homologous cell is sometimes non-permissive (non-virogenic), but frequently enough, it is permissive (virogenic). In the permissive phase, the virus is transmitted both vertically and the production of viral particles requires the intervention of an auxiliary or “helper” virus (leukemogenic virus) that replicates in the transformed cell both the code of its own shell and that of the defective virus. The transformed cell produces both leukemogenic viruses and pseudotypes of defective sarcomatogenic viruses (viral particles that possess the genome of the sarcomatogenic virus and the helper virus shell).

The main oncogenic viruses are: deoxyviruses or DNA viruses and riboviruses or RNA viruses. Deoxyribovirimes, also called oncornaviruses, form a heterogenous group including: poxviruses, adenoviruses, papovaviruses and herpes-viruses.

Oncogenic viruses known as tumor inducers in animals can be grouped as follows:

- **Herpesviridae:**
  - the Marek disease virus induces malignant lymphomas in chickens;
  - herpes virus saimiri induces reticulosarcomas in chimpanzees;
  - the bladder carcinoma virus induces adenocarcinomas in frogs;
  - the pulmonary adenomatisis virus induces pulmonary carcinoma in sheep.

- **Papoviridae:**
  - the bovine papillomavirus induces cutaneous papillomatosis in cattle;
  - the equine papillomavirus induces sarcomas in horses;
  - the rabbit papillomavirus induces Shope papilloma and in domestic rabbits, carcinomas.

- **Polyomavirus:** it induces sarcomas in mice.

- **Retroviridae:**
  - Type C oncornavirus:
    - the feline leukemogenic virus induces lymphosarcomas in cats;
    - the feline sarcoma virus induces fibrosarcomas in cats;
    - the bovine leukosis virus induces lymphoid leukosis in cattle;
    - the avian leukosis virus induces lymphoid leukosis in chicken.

  - Type B oncornavirus: the mouse mammary tumor virus induces adenocarcinoma in mice

Other Virus includes,

- RNA Virus
- DNA Virus
- Myxovirus
- Polyma virus
- Chicken sarcoma
CARCINOGENESIS AND ITS MECHANISMS

In 1969, FOULDS had the intuition in the natural history of cancer of its stage evolution, and in 1982, BERENBLUM established three distinct stages: the initiation stage, the promotion stage and the progression stage. If the first two stages underlie the triggering of cell transformation, the third stage determines the transformation of a benign tumor into a malignant form, with the maintenance and evolution of malignancy.

The theories of carcinogenesis can be grouped as follows: the genetic mutation theory, the aberrant differentiation theory, the viral theory and the cell selection theory. A theory that is unanimously accepted at present is the multistage theory.[15]

THE GENETIC MUTATION THEORY

As early as 1987, HANSEMANN remarked the analogies between mutation and cancer; both are hereditarily transmitted to the daughter cells. According to this theory, the origin of cancer is due to structural anomalies of the genes that regulate cell growth and differentiation. Genetic changes can be hereditary or they can occur in the course of life under the carcinogenic action of various pathogenic factors. In this sense, the following arguments can be mentioned:

- The influence of genetic constitution in the appearance of cancer; chromosomal anomalies are frequently associated with malignant tumors. Chromosomal anomalies associated with malignant tumors are known: Down syndrome (trisomy 21) and Klinefelter syndrome (XXY), associated with leukemia; D deletion syndrome (deletion of the long arm of chromosome 13), with retinoblastoma; Philadelphia chromosome (22-9 translocation) and chronic myeloid leukemia; the presence of hereditary cancer – the susceptibility to a number of tumor locations is transmitted as a hereditary dominant character. These hereditary cancers seem to evolve along two stages: an inherited mutation, followed by a mutation acquired in the course of life. This group of tumors includes: Wilms tumors, retinoblastomas, neuroblastomas and very likely mammary, endometrial, colon cancer, and leukemia;

- The presence of chromosomal anomalies in the cancerous cell has been detected in almost all malignant tumors. Initially, the karyotype of the tumor cell tends to be unstable and variable, but it gradually stabilizes in a highly aneuploid form;

- The correlation between mutagenicity and carcinogenicity: the more mutagenic an agent, the more likely it is to be carcinogenic; it is the case of ionizing radiations, alkylating agents and polycyclic hydrocarbons.

In addition to these possibilities of genetic mutations by external factors, spontaneous mutations also occur. In the etiology and pathogenesis of some cancers, a determining factor is represented by endogenous processes that can induce phenomena of intrinsic mutagenesis. A mutational cause of malignancy supposes that among the mutations dispersed throughout the genome there are key-genes that modify the properties of cells, allowing them to escape from the homeostatic mechanisms that regulate cell division, by invasion and metastasis. Spontaneous mutation is the consequence of
lesions that must occur frequently enough to overcome the capacity of the cell to repair the damaged DNA. Spontaneous mutations can be the result of errors caused by DNA polymerases, during DNA replication. Spontaneous mutations can have the same cancer inducing potential as those caused by environmental exogenous agents.

Assuming that a single dominant mutation is oncogenic, the spontaneous mutation rate is sufficient to produce millions of cancerous cells in the course of life. Numerous mutations with cancer inducing potential may have no effect, since cell proliferation is controlled by homeostatic mechanisms that govern the growth and behavior of cells. Multiple and sequential mutagenic events are necessary to initiate carcinogenesis. A mutant phenotype can result from genetic mutations, such as DNA-polymerase, with the production of a modified enzyme that is exposed to errors in the catalysis of DNA synthesis. A mutant phenotype explains chromosomal instability which, as it is known, characterizes tumor progression.

Taking into consideration the extremely high number of proteins involved in DNA replication and repair, it may be concluded that the number of potential targets that can generate mutant phenotypes can be higher than the number of oncogenes known.

**Potential sources of spontaneous mutations:**

1) chemical DNA instability – among covalent changes, depurine is the most frequent; DNA-polymerases – seem to frequently meet abasic positions, which is why the replication and the mismatch incorporations on the opposite side of these loci is a major source of spontaneous mutations;

2) mutagenesis by free oxygen radicals occurs especially through hydroxyl ions that seem to be the most damaging; the free radicals resulting from oxygen metabolism change the RNA, membrane proteins and DNA. DNA lesions occur frequently enough to represent a source of spontaneous mutation;

3) due to errors in DNA replication, mutagenesis takes place through the erroneous replication of nucleotides, which are by definition mutations; the priority of DNA-polymerase in ensuring DNA replication is proved by genetic studies, and the errors caused by DNA-polymerase increase mutagenesis

The acceptance without reserves of spontaneous mutagenesis as an oncogenic factor might lead to the fatalist conclusion that the appearance of numerous cancers is inevitable. **The aberrant differentiation theory** maintains that the origin of cancer is secondary to functional disorders of genetic regulation mechanisms, without structural changes, which explains the designation of this theory as epigenetic theory. It has been experimentally demonstrated that tumor cells of different origins introduced in a fetal environment have led to the resumption of the tumor cell differentiation process, with the loss of the malignant phenotype, as a result of the cell-cell contact or through mediators present in the extracellular environment (PITOT et al., 1985). These experiments suggest that the neoplastic cell phenotype can be considered the consequence of a reversible disturbance in the genetic region and not necessarily a mutation, at least for some tumor processes.

**The viral theory** of the origin of cancer has stimulated the study of the proliferation mechanisms of normal and tumor cells, leading to the discovery of viral oncogenes, capable of malignant transformation, and their normal
homologues, the protooncogenes. Viral oncogenes act in the nucleus, the cytoplasm and at the cell membrane surface. Their action is carried out by: phosphorylation, initiation of DNA synthesis and transcription regulation\(^7\).

According to HUBNER and TODARO (1969), the majority of vertebrates have oncomavirus genomes integrated in their genetic patrimony, which are automatically transmitted to their descendants by means of germ cells. These viral germs remain inactive for a certain time, being under the dependence of regulating genes, and only manifest after the intervention of depressive factors. The authors suggest the existence of two distinct viral genes, the virogene and the oncogene. The virogene is involved in the replication and release of the virus; at the same time, some cellular genes can modulate the activation of the virogene. The oncogene commands the cell transformation process.

Researches of the relation between cancer and virus have led to the discovery of the cellular oncogene. Incorporated in the genome of a “lending” oncomavirus, these genes acquire carcinogenic potential. The result can be the same if the cellular gene is depressed before the action of mutagenic differentiations on latent regulating genes.

The discovery of cellular oncogenes has allowed the unitary theory of carcinogenesis, which explains why extremely different agents, such as viruses, radiations, chemical substances, etc. cause the same cellular changes, with carcinogenic effects.

The cell selection theory considers cancerization as a result of the selection of a cellular population with increasing autonomy and malignancy, which has gradually adapted to environmental conditions. This theory ignores or minimizes the important role of mutations occurring throughout the duration of the neoplastic process.

The cell selection theory, with all its implications in the appearance and evolution of the neoplasm, is developed in the chapter on tumor generalization and metastasizing.

MULTISTAGE CARCINOGENESIS THEORY

This theory seems to be generally accepted. Carcinogenesis is a multistage process, since between the initial carcinogenic stimulus and the final manifestation of cancer there are several stages (HART and TURTURRO, 1988\(^8\)).

The period between the fixation of a carcinogen to chromosomal DNA and the appearance of a population of neoplastic cells can be divided in the following stages: initiation, promotion and progression\(^8\).

INITIATION

This stage starts with the action of the carcinogen on chromosomal DNA, inducing a lesion, which can be repaired or reproduced.

The biological mechanisms of repair are complex, and possibilities of action for short and long repair are known. Thus, a lesion can be identified by a specific endonuclease that dissects the damaged filament, a DNA-polymerase is fixed at the level of the dissection and ensures synthesis using as a model the intact complementary filament, and a polynucleotideligase allows the fusion of the repaired segment and the rest of the filament.

Other enzymes can act for the excision of a changed single base: N-glycosylase, AAE (apurinic-acid-endonuclease and apyrimidinic-acid-endonuclease), exonuclease, DNA-polymerase, lygase, etc.

Postreplication repair. During DNA replication, DNA-polymerase “skips” the injured
area that cannot be replicated. The integrity of the newly synthesized filament is restored by an exchange of genetic material between homologous filaments. The gap involving the donor filament will be filled by the intervention of a DNA-polymerase able to replicate an intact complementary filament. In the repair of a cell lesion, the time factor is essential. Thus, if mitosis is delayed, DNA can be repaired; if not, the lesion will be replicated and transmitted to the new cells.

The initiation stage of a cell starts with the impossibility of repairing of the DNA lesion. The initiation of a cell involves its genetic compatibility with the activation of different carcinogenic factors that can act alone or in association, in an isolated way or along several stages. Genotoxic factors can be of different kinds: viruses, radiations, chemical substances, etc. Carcinogenic factors have, according to BERENBLUM’s scheme (1982), an irreversible genotoxic action; repair processes do not occur.

Initiation confers the cell proliferative capacities that remain potential, latent, without necessarily leading to the promotion stage. Following the action of chemical, physical or biological factors, the initiated cell presents an irreversible alteration of the genetic material and has the potential to develop a neoplastic cell clone. Initiation represents a rapid process, of the order of minutes or hours, and the initiated cell can remain indefinitely in this state, without producing adverse effects and without being recognized by the defense systems of the organism, since it does not manifest phenotypically19.

**PROMOTION**

Chronic genetic alterations of the initiated cell determine the neoplastic transformation and the appearance of cells that are capable of autonomous growth. The promoter (noncarcinogenic or weakly carcinogenic if used alone) is applied several times after the simple administration of an initiating carcinogen. “Complete” carcinogens are also known; these agents, with certain doses and application modes, induce cancer without the need for the subsequent action of a promoter. Promoters act by the alteration of normal growth processes, by mechanisms similar to hormonal or growth factor mechanisms.

Experimental carcinogenesis studies have proved that the promotion stage presents a first reversible phase and a second irreversible phase.

Tumor promotion is to a great extent, perhaps even totally, associated with epigenetic factors that alter, directly or indirectly, the genomic DNA expression20. Promotion would consist of events occurring in the genetic program of terminal proliferation and differentiation. The promoted cell does no longer recognize the differentiation signals, which would normally remove it from the replication population. Unlike initiators, promoters do not bind to DNA, their major target being the cell membrane.
Progression is characterized by marked malignancy and the tendency to induce changes that cause the death of the host. Cells in the progression stage are characterized by genetic changes, gene alterations and rearrangements, even karyotype alterations, and the tumor is phenotypically characterized by a rapid proliferation rhythm, invasive and metastasizing properties, with biochemical and morphological changes. The essential characteristic is the extraordinary instability of the karyotype. In the study of tumor progression, 5-ase-cytidine was observed to have variable effects, being able to activate (onco)genes involved in the progression process, and in other cases to activate oncogene suppressor genes (antioncogenes)\(^2\).

Carcinogenesis appears as a multistage process at molecular level, being triggered either by the action of retrovirus oncogenes, which all induce RNA synthesis and cell division, or by the disturbed, abnormal activity of protooncogenes, one cellular oncogenes\(^3\).

**Multistage carcinogenesis theory** :-

Studies have shown that there are genetic mechanisms involving hereditary transmissible DNA alterations, as well as epigenetic mechanisms that involve the expression of one or several genes. Genetic mechanisms have been demonstrated by the presence of hereditary cancer or by the increased incidence of cancer in congenital chromosomal lesions or in disorders characterized by DNA repair deficiencies.

The evolution of a normal cell towards a cancerous cell is a complex process, which involves multiple stages, leading to the appearance of a clone of cells that no longer have the same control possibilities as normal cells. SPANDIDOS and ANDERSON (1989) mention three main classes of genes:

1. **oncogenes**, which derive from altered normal genes, protooncogenes, so that they become activated\(^2\),
2. **modeling genes**, which can predispose to cancer and are submitted to a mutation. In general, there is a group of heterogeneous genes, some of which are involved in the repair of damaged DNA;
3. **oncosuppressor genes**, also known as: antioncogenes, tumor suppressor genes or emerogenes. The whole group has the property of inhibiting the cancer phenotype. The mode of functioning and identification of oncosuppressor genes is difficult; it seems that their role is to inhibit cell
proliferation, not to directly regulate oncogenes.

REFERENCE


20) Yamasaki H, Multistage carcinogenesis: implications for risk


