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Chemical Carcinogenesis: Risk Factors, Early Detection and Biomedical Engineering

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1. Introduction

Cancer is now recognized in both humans and in other multicellular animals as arising from a number of different causes, including specialized viruses, radiation, chemicals, certain highly irritative parasites (inflammation) and a number of other factors, such as specific genetic defects present in individual humans and possibly in every member of a colony of specially bred animal models. Cancer from non genetic causes largely from environmental factors, of which chemicals have a disproportionate share, is believed to contribute nearly 70% of all cancer cases. Chemical carcinogenesis originally derives from experimental induction of malignant skin tumor in mice with chemicals. Early studies indicated some agents such as polycyclic aromatic hydrocarbons (PAH) could cause cancer of the skin if they were painted on to mice in high doses. These early studies also showed that the induction of cancer was dose dependent; in low dosage they would not cause cancer but would render the skin susceptible to developing cancer on exposure to another agent, which, on its own would not induce cancer.

Thus at the dawn of the 20th century, it was recognized that chemicals cause cancer; though individual cancer causing molecules had not yet been identified, nor their cellular targets clearly known. It was however clearly understood that carcinogenesis, at the cellular level, was predominantly an irreversible process. Knowledge of the mechanisms by which chemicals cause cancer and the molecular changes that characterize tumor progression was lacking. The origin of the understanding that cancer had a cause was first pointed out by the Italian investigator, Ramazini in 1700. Seven and a half decades later, the British Surgeon, Percival Pott made the connection between exposure to soot, rich in hydrocarbons and scrotal cancer (Pott, 1775). It is now known that at the most fundamental level, cancer is caused by abnormal gene expression. This abnormal gene expression occurs through a number of mechanisms, including direct damage to the DNA, and inappropriate transcription and translation of cellular genes. The contribution of chemicals to the carcinogenic process is well known to have increased given the parallel between industrialization with associated increased chemical production and utilization and the prevalence of cancer.

Increasing use of chemicals, particularly in the industrializing developing countries (Pakin et al., 1993; Pearce et al., 1994) places new demands on these countries, as they have limited resources to adequately regulate exposure to chemicals. Majority of the chemicals cause mutation in DNA among others. The consequences of increased exposure to chemicals, risk of cancer, early detection of chemical-induced neoplastic changes and the prominent role of biomedical engineering is poorly recognized generally and particularly in the developing countries where chemical carcinogenesis is believed to be currently more prevalent (Huff and Rall,1992). Cancer is classically viewed as the result of series of mutations, including dominantly acting oncogenes and recessively acting tumor- suppressor genes. Each mutation leads to the selective overgrowth of a monoclonal population of tumor cells, and each significant tumor property (invasiveness, metastasis and drug resistance) is accounted for by such mutation (figure 1). The seminal observation that carcinogenesis is a multistage process helps to explain why some chemical carcinogens lack apparently important properties exhibited by others. Such agents may act as promoters on tissues that have been previously initiated or have the ability to produce naturally occurring tumors without treatment.

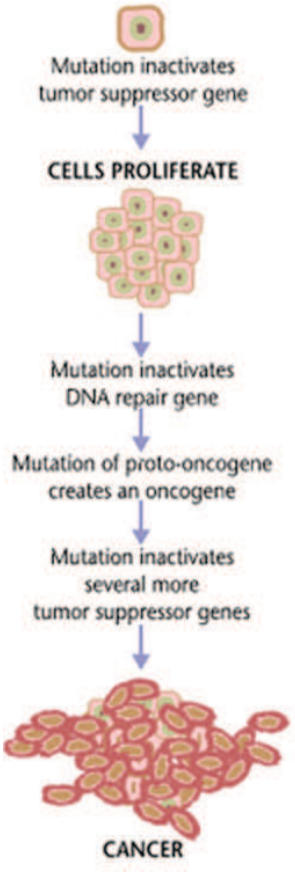


Fig. 1. Stages of the carcinogenic process

DNA-reactive	Activation-independent	Nitrogen mustards, chlorambucil
		Alkylating agents
		Epoxides: ethylene oxide
	Activation-dependent	Aliphatic halides: vinyl chloride
		Aromatic amines: monocyclic-o-toludine; polycyclic-4-aminobiphenyl, benzidine
		Nitroaromatic compounds: 1-nitropyrene, 3-nitrofluoranthene
		Heterocyclic amines: 2-amino-3-methylimidazo [4,5-b]pyridine(Ph1P)
		Aminoazo dyes: dimethylaminoazobenzene
		Polycyclic aromatic hydrocarbons: benzo(a)pyrene
		Substituted polycyclic aromatic hydrocarbons: 3-methlycholanthrene
		N-nitroso compounds: dialkyl-dimethylnitrosamine, diethylnitrosamine; cyclic-
		N-nitrosonornicotine (NNK), nitrosomorphaline triazines, hydrazines,
		azoxymethane, methylazoxymethanol, benzene
		Mycotoxins: aflatoxin B1, aflatoxin G1
		Plant products: pyrrolizidine alkaloids, aristolochic acid, cycasin
		Pharmaceuticals: cyclophosphamide, phenacetin, tamoxifen
Epigenetic	Promoter	Liver enzyme-inducer type hepatocarcinogens: chlordane, DDT, pentachlorophenol, phenobarbital, polybrominated biphenyls, polychlorinated biphenyls
		Kidney: nitrilotriacetic acid
		Bladder: sodium saccharin
		Forestomach-butylated hydroxyanisole
	Endocrine-modifier	Hormones: estrogens-17-estradiol; catechol estrogens-4-hydroxy-estradiol, 2-hydroxyestradiol
		Estrogen agonists: 17-ethinyl estradiol, diethylstillbestrol (DES)
		Prolactin inducers: chloro-s-triazines-atrazine
		Antiandrogens: finasteride, vinclozolin
		Antithyroid thyroid tumor enhancers
		Thyroperoxidase inhibitors: amitrole, sulfamethazine
		Thyroid hormone conjugation enhancers: phenobarbital,
		Gastrin-elevating inducers of gastric neuroendocrine and glandular tumors: lansoprazole,omeprazole, pantoprazole
	Immunosuppressor	Cyclosporin
		Purine analogs
	Cytotoxin	Mouse forestomach toxicants: propionic acid, diallyl phthalate, ethyl acrylate
		Rat nasal toxicants: chloracetanilide herbicides
		Rat renal toxicants: potassium bromate, nitrilotriacetic acid
		Male rat kidney _2u-globulin nephropathy inducers: D-limonene, p-dichlorobenzene
	Peroxisome proliferator	Hypolipidemic fibrates: ciprofibrate, clofibrate, gemfibrozil
		Phthalates: di(2-ethylhexyl)phthalate(DEHP), di(isononyl)phthalate
		Lactofen
Minerals and Metals		Minerals: asbestos
		Metals: arsenic, beryllium, cadmium, chromium (IV), nickel, silica
Unclassified		Acrylamide, acrylonitrile, dioxane

Table 1. Classification of chemicals with carcinogenic activity

Foulds (1969) suggested that cancer development consisted of three, rather than two processes: (1) initiation, or the conversion of normal cells to a potentially precancerous form (2) promotion, or the expansion of the clones of initiated cells to form tumors; and (3) progression, or the development of tumors to increasing levels of malignancy. The original view was based on Foulds' wealth of experience with both clinical and experimental cancer. It has however, been expanded greatly since it was first propounded by Foulds (1982). Other investigators have also made significant contributions to the understanding of the process of carcinogenesis by suggesting that there are two major cell-based processes essential to the formation of tumors (Ames and Gold, 1981).The first, or initiating stage, is due to mutation; alteration of the DNA of the affected cell through permanent modification of the DNA. These mutations take place at specific locations on the DNA, referred to as oncogenes and tumor suppressor genes, if these individual cells are to serve as precursors of cancer (Willis, 1960; Klein and Klein, 1984). This area remains intensely investigated in the last couple of decades. What is perhaps worthy of note is that while the activation of an oncogene requires mutation at a specific single base (arrangement of the amines making up the DNA) pair on the DNA template, inhibition of a tumor suppressor gene may be achieved by a much wider range of damaging interactions.

In current research, emphasis is laid on the identification of the genes that are involved in the mutation and subsequent molecular events. The failure in the control mechanisms regulating the expression of and response to tissue growth factors is of considerable interest in chemical carcinogenesis. This contributes to the risk of chemical carcinogenesis and is in turn attributable to a number of factors that will be discussed subsequently. A critical process in carcinogenesis is promotion. This involves cellular proliferation, which involves the division of cells to form two unusually identical cells. This may increase the number of both "normal" and neoplastic mutated or preneoplastic cells, enhancing the chance of a tumor being expressed in a clinically observable form. Surprisingly, such increased levels of cellular proliferation may not be apparent in normal cells of a particular tissue but may occur only in pretumor cells thus making early detection difficult. Tumors are well known to increase in their degree of malignancy with time, a process named "progression" by Foulds. Cohen and Elwein (1991) have suggested that progression is the result of a cascade of further critical mutations in the neoplastic cell population followed by further cell proliferation to increase the number of genetically altered cells and the chance of their forming an increasingly malignant, clinically apparent cancer.

2. Summary of stages of chemical carcinogenesis

Studies indicate that three stages of chemical carcinogenesis can be defined; initiation, promotion and progression as briefly alluded previously.

Initiation: This is concerned with the induction of genetic changes in cells, leading to genome instability. This can be accentuated by micronutrient deficiency disorders. The nature of the initial changes is still incompletely elucidated (Satoh, 1988)

Promotion: This largely involves the induction or commencement of cell proliferation. In this phase of carcinogenesis a promoting agent or enabling microenvironment, brings about increased cell proliferation. This stage is very important as it is reversible if the promoting agents or risk factor(s) are withdrawn. Probably also, if some genome stabilizing micronutrients are abundant. This stage has been exploited considerably for both therapeutic and chemopreventive measures that are in part dependent on micronutrients.

Progression: If cell proliferation is sustained then initiated cells acquire secondary genetic abnormalities in oncogenes which first lead to dysregulation and finally to autonomous growth characteristic of cancer. The ultimate end-point of progression is development of invasive neoplasm.
While many environmental agents can be considered to be chemical carcinogens; some act as both initiators and promoter (complete carcinogens). The understanding of molecular aspects of chemical carcinogenesis has lead to development of the concept of chemoprevention (anticarcinogenesis). This process proposes strategies for intervention at the phase of malignancy using drugs or natural or synthetic agents to reverse or halt the evolution of carcinogenesis which is dependent on recognition of risk factors and early detection.

2.1 Brief history of chemical carcinogenesis

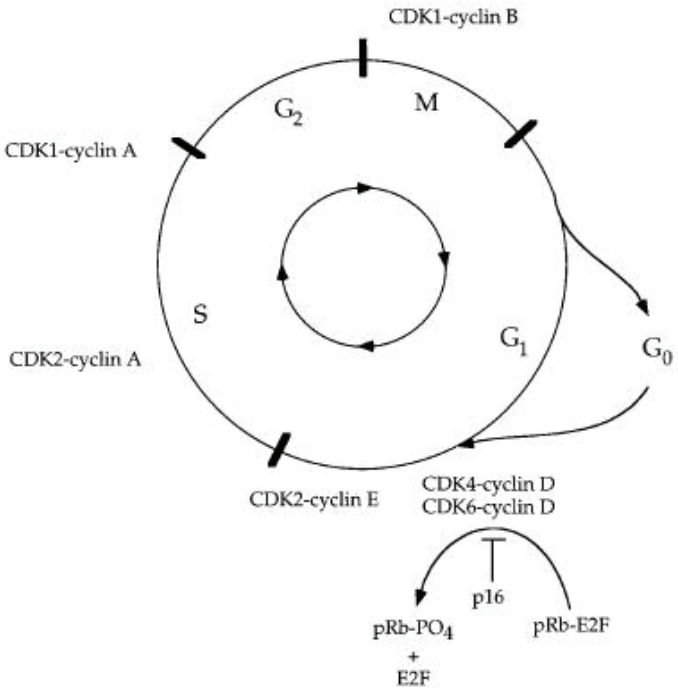
The history of chemical carcinogenesis is punctuated by key epidemiologic observations and animal experiments that identified cancer-causing chemicals and that led to increasingly insightful experiments to establish molecular mechanisms and to reduction of human exposure to chemicals. In 1914, Boveri (1914) made key observations of chromosomal changes, including aneuploidy. His analysis of mitosis in frog cells and his extrapolation to human cancer is an early example of a basic research finding generating an important hypothesis (the somatic mutation hypothesis). The first experimental induction of cancer in rabbits exposed to coal tar was performed in Japan by Yamagiwa and Ichikawa (1918) and was a confirmation of Pott's epidemiologic observation of scrotal cancer in chimney sweeps in the previous century (Potts, 1775). Owing to the fact that coal tar is a complex mixture of chemicals, a search for specific chemical carcinogens was undertaken. British chemists, including Kennaway (1930), took on this challenge and identified polycyclic aromatic hydrocarbons (PAHs), such as, benzopyrene, which was shown to be carcinogenic in mouse skin by Cook and his colleagues in 1933. The fact that benzopyrene and many other carcinogens were polyaromatic hydrocarbons lead the Millers (1947) to postulate and verify that many chemical carcinogens required activation to electrophiles (electron seeking moieties) to form covalent adducts with cellular macromolecules. This in turn prompted Conney and the Millers (1956) to identify microsomal enzymes (P450s) that activated many drugs and chemical carcinogens.

3. Cell regulatory mechanisms: The cell cycle

Carcinogenesis, or the sequence of events leading to cancer, is a multistep process involving both intrinsic and extrinsic factors. In the normal tissue, there are numerous regulatory signals that instruct cells when to replicate and when to die. In a cancer cell these regulatory mechanisms become disabled and the cell is allowed to grow and replicate unchecked. Thus at the most fundamental level cancer is caused by abnormal gene expression. This abnormal gene expression occurs through a number of mechanisms including direct damage to the DNA, and inappropriate transcription and translation of cellular genes. Carcinogenesis has been demonstrated abundantly to be induced or at least caused by exposure to certain types of chemicals (carcinogens). The mechanisms are elaborated on subsequently. The cell cycle plays an important role in this regard. It is concerned with the processes that govern the life and death of cells and through transient delay in G_0 phase or outright apoptosis (programmed cell death) might be able to prevent damage in the DNA of a cell that may proceed to

carcinogenesis. In the normal cell, replication of the DNA and cell division is stimulated by the presence of growth factors that bind receptors at the cytoplasmic membrane and initiate a cascade of intracellular signals. Once these signals reach the nucleus they induce transcription of a complex array of genes producing proteins that mediate progression of the cell cycle culminating in mitosis or cell division. One remarkable contribution of biomedical engineering is the introduction of flow cytometer equipment which enable stages of the cell cycle to be followed and disorders or disruptions there of detected.

The cell cycle is conventionally divided into four (4) phases, although there is the subsidiary G_0 phase. The duration of each of these phases varies depending on factors such as cell type and localized conditions within a given tissue (microenvironment). At the end of mitosis (M) daughter cells enter gap 1 (G_1) phase.



A schematic representation of the mammalian cell cycle. In each cell division cycle, chromosomes are replicated once (DNA synthesis or S-phase) and segregated to create two genetically identical daughter cells (mitosis or M-phase). These events are spaced by intervals of growth and reorganization (gap phases G_1 and G_2). Cells can stop cycling after division, entering a state of quiescence (G_0). Commitment to traverse an entire cycle is made in late G_1. Progress through the cycle is accomplished in part by the regulated activity of numerous CDK–cyclin complexes, indicated here and described in the text.

Fig. 2. Schematic representation of Cell Cycle.

If conditions are favourable cells enter the synthetic (S) phase of the cycle where the entire genome is replicated during DNA synthesis. Following 'S' phase, cells enter the gap 2 (G_2) phase before proceeding through mitosis again. A critical phase boundary exists early in the G_1 phase called the restriction point. This is the point at which the cell must decide to either enter the cell cycle once more or to secondly move into a state of quiescence; G_0 phase. Once committed to this pathway, the cell can either remain in this state of replicative quiescence until it receives a signal to divide again. Alternatively the cell can proceed down a path that leads either to terminal differentiation or to apoptosis. Movement of a cell through the cell cycle is regulated by an enormously complex array of proteins.

The proteins include:

- Cyclins
- Cyclin dependent kinases (CDKs)
- Cyclin activating kinases (CAKs)
- CDK inhibitory proteins.

Binding of an appropriate growth factor at the cell surface starts a signaling cascade that ultimately leads to the expression of the G1 phase cyclins. It is important to remark that in normal cells, external stimuli (factors) such as growth factors are absolutely needed for the cell to proceed beyond the restriction point. Beyond this point, the cell is committed to DNA replication and cell division. Interference with the normal signal transduction pathway by chemical carcinogens, the mechanism notwithstanding can transform a cell into a state of proliferation that is not regulated by normal physiological controls (carcinogenesis). This basically is broadly the molecular basis of carcinogenesis.

Table 2. Proteins Controlling the Cell Cycle.

It is note worthy that all phases of the cell cycle are regulated by the micronutrient zinc. Thus zinc deficiency common in many developing countries (WHO, 2002; Ames, 2010) can be risk factors in chemical carcinogenesis. Ho et al (2003) have elegantly demonstrated this in their studies. This is an area where biomedical engineering has contributed significant in the last five or more decades by the production of flame absorption spectrophotometers (FAAS) and later the graphite furnace (carbon rod) (GFAAS). This was followed by inductively coupled plasma mass spectrometer which allows for simultaneous multi element analysis. These equipment have exquisite sensitivities which enable the status of zinc and many other micronutrients to be detected and indirectly play a preventive role; reducing risk of cancer.

4. Molecular biology and chemical carcinogenesis

The discovery of DNA as the genetic material by Avery, MacLeod, and McCarthy (1944) and the description of the structure of DNA by Watson and Crick (1953) indicated that DNA was the cellular target for activated chemical carcinogens and that mutations (alterations in the sequence of bases making up amino acids) were key to understanding mechanisms of cancer. This led to defining the structure of the principal adducts in DNA (complexes of

DNA and a carcinogen or its metabolite) by benzo (*a*) pyrene (Carrel et al., 1997) and aflatoxin B_1 (Croy et al., 1978). The concepts developed in investigating mechanisms of chemical carcinogenesis also led to discoveries that are relevant to other human conditions in addition to cancer, including atherosclerosis, cirrhosis, and aging. The fact that genetic changes in individual cancer cells are essentially irreversible and that malignant changes are transmitted from one generation of cells to another strongly points to DNA as the critical cellular target modified by environmental chemicals. DNA damage by chemicals occurs randomly; the phenotypes of associated carcinogenic changes are determined by selection.

Epidemiologic studies from all over the world have identified environmental and occupational chemicals as potential carcinogens. The most definitive epidemiologic studies have been those in which a small group is exposed to a tremendously large amount of a specific chemical, such as aniline dyes. The table below (table 3) lists some of the fairly well characterized chemicals sites where they have induced cancer.

Carcinogens		**Site of cancer**
Chemical mixtures	Soots, tars, oils	Skin, lungs
	Cigarette smoke	Lungs
Industrial chemicals	Benzidine	Urinary bladder
	Nickel compound	Lungs, nasal sinuses
	Arsenic	Skin, Lungs
	Vinyl choride	Liver
Drugs	Mustard gas	Lungs
	Phenacetin	Renal pelvis
Naturally occuring compounds	Cyclomates	Bladder
	Nitroso compounds	Oesophagus, Liver, Kidney, stomach

Table 3. List of Chemical Carcinogens.

5. Mechanisms of chemical carcinogenesis

As part of daily existence, DNA frequently sustains damage. If unrepaired, this can lead to mutations that replicate resulting in abnormal and cancerous development. Some biological mechanisms usually inhibit this process. An enzyme 8-oxoguanine DNA glycosylase (OGG1) among others repairs DNA by excising damaged nitrogen bases constituting the DNA. DNA damage may occur through exposure to chemicals present in cigarette smoke, ionizing radiation and oxidative stress, which can be induced by a number of chemicals such as cadmium and the polycyclic aromatic hydrocarbons. The levels of OGG1 can thus be used to predict an individual's risk of developing cancer.

At least four fundamentally different mechanisms of cancer induction by chemicals have been identified. These may lead to cancer as individual processes or on occasion, the same agent may exert its effects through two or more processes to lead to tumor formation. The importance of the mutation/proliferation approach to the development of cancer lies in its ability to encompass each of these mechanisms within a single frame work. This as has been demonstrated (Clayson, 2001), means that if we can measure changes in mutation and proliferation frequencies, due to a specific carcinogen, there may be no need to elucidate the detailed mechanism of carcinogenesis for every chemical carcinogen before attempting to calculate accurately the risk it may carry for exposed human subjects. This requires exquisite

and very sensitive instruments, and appears to be one challenge to specialists in biomedical engineering. Fortunately by the wide range of flow cytometry and mass spectrometry based techniques, the field of biomedical engineering appears to be rising to the challenge. It needs not be emphasized that a great deal of thought and effort will be required if mutation rates and proliferation in specific cell types are to be measured in humans by non-invasiveness.

A number of chemical carcinogens now appear to exert their primary effect on the mutational part of the carcinogenic process, while some others seem to be relatively devoid of the ability to interact with DNA and appear to work mainly through a mechanism of induction of cellular proliferation. Mutation on the other hand appears to be induced by chemical carcinogens by at least two major modes. The modes involve direct interaction with the DNA through the formation of highly reactive, positively charged entities known as "electrophiles" This entity is capable of reacting chemically with many different cellular constituents, including the genetic material, DNA (Miller et al, 1961). The adducts formed with DNA the interaction products of such carcinogen-derived electrophiles with DNA, are not regarded as genetic lesions in their own right. They only represent the first stage in the formation of a mutational event. The adducts may be effectively repaired by the DNA repair enzyme system found in the cell nucleus as earlier indicated. In the alternative, if they are not repaired they may affect important sites on the DNA and consequently die, or if the DNA replicates while they are still present, may lead to mutations through base-mispairing or other errors, that is culminating in true genetic lesions. This has been broadly illustrated by the figure below (figure 3).

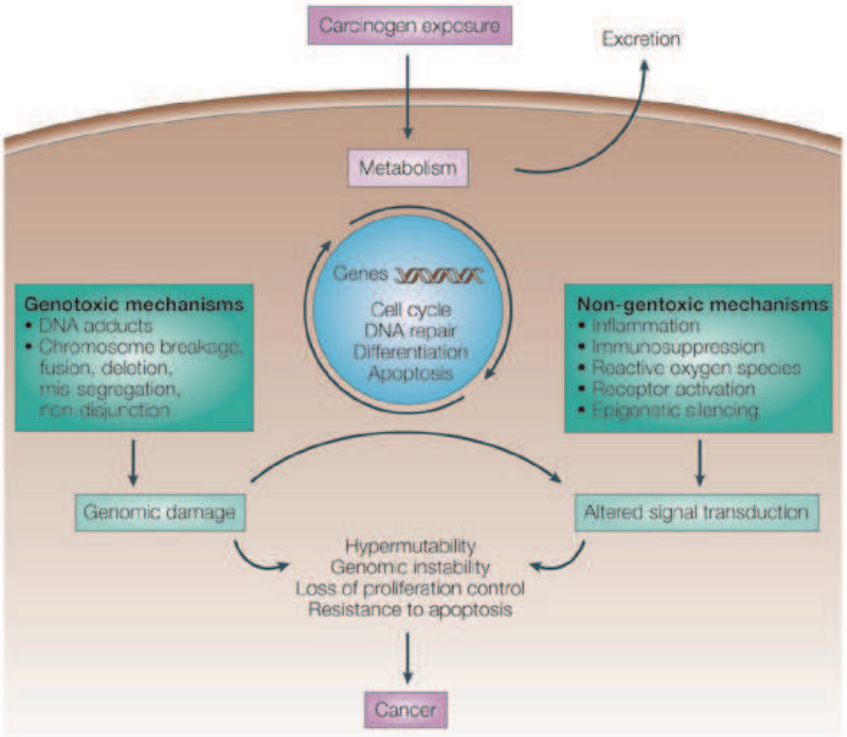


Fig. 3. Overview of genotoxic and non-genotoxic effects of carcinogens.

If the induced mutations occur at one or a relatively few critical sites on the DNA, then the cells may be converted from a "normal" to a preneoplastic state. Chemically-induced mutations are not limited to critical genes, different pretumor cells may demonstrate a variety of different growth potentials due to the range of altered " non-critical" genes, thus enabling those cells with most favourable properties to transform most rapidly to clinically apparent tumours. Alternatively, the carcinogens may act indirectly through the formation of reactive oxygen species or nitrogen radicals, some types of which are also highly reactive with macromolecules such as DNA. The process of raised cellular proliferation is also multi-factorial in its genesis. It may arise from, for instance, direct hormone-like stimulation of specific cell types, from perturbation of tissue processes that lead to a balance between cell proliferation and cell death (apoptosis), it may alternatively arise from massive cell-killing or cytotoxicity followed by proliferative regeneration to maintain the physiological functioning of the affected tissues. A yet further way by which excess, tumor-inducing cellular division may be induced is that exhibited by the urinary bladder. Oyasu and his colleagues (1981) and in his subsequent studies (1995) showed by using heterotopical transplant rat bladder technique that urine by itself, but not water can induce proliferation. The mechanism by which this happens is not quite clear.
It was however conceived that urine contained epithelial growth factors that stimulate cell division and that such factors would penetrate the epithelium should it be injured by the presence of a foreign agent in the bladder. A fourth type of mechanism of carcinogenesis may arise from the ability of the agent to form a complex with a specific protein. This complex (ligand-protein) may have the property of altering the expression of specific and important region in the DNA. There is the emerging but incompletely understood involvement of epigenetics; alteration in the genetic processes not involving DNA base sequence. Many epimutagens have already been identified and a number of existing chemicals such as cadmium are also known to act through this pathway.

6. The environment and cancer

Cancers caused by environmental agents frequently occur in tissues with the greatest surface of exposure to the agents: lung, gastrointestinal tract, and skin. Recently, the study of chemical carcinogenesis has merged with studies on the molecular changes in cancer cells, thus generating biological markers to assess altered metabolic pathways and providing new targets for therapy. Although these are exciting areas, they may be peripheral to attacking the primary causes of the most common human cancers. As more and more mutations are catalogued in cancer cells and more and more changes in transcription regulation, it becomes increasingly apparent that we need to understand what generates these changes. The fact that chemicals cause random changes in our genome immediately implies that our efforts need to be directed to quantifying these changes, reducing exposure, and developing approaches to chemoprevention (Extensively reviewed by Pereira, 1997).

7. Mechanism of oxidative stress and DNA damage due to micronutrient deficiency

Micronutrients are referred to as nutrients required in very small amounts that do not have calorific values but are extremely important for the maintenance of health. They comprise the vitamins and trace elements that regulate vital metabolic and molecular pathways and

processes. Some of them play very vital roles in DNA and RNA metabolism either as coenzymes or cofactors involved in their metabolism or as components of systems intimately interacting with these molecular regulators. The micronutrients are basically supplied in the diet or may be taken as supplements. Very few of them are synthesized endogenously enough to meet physiological requirements hence they are mostly essential.
Based on public data emanating from the Healthy People 2010 Project, it has been estimated that about 80% of colon and prostate cancers, may be influenced by diet, nutrition, and life style. It has been proposed that DNA damage induced by dietary micronutrient deficiency accounts for about 33% of preventable cancers (Ames, 2001; Ames and Wakimoto, 2002). Owing to the fact that micronutrient deficiencies can induce DNA damage in a manner similar to those induced by ionizing radiation and reactive oxygen species (ROS), it has been suggested that oxidative stress and the associated DNA breaks are critical targets for nutritional control of carcinogenesis (Cheng, 2009) and perhaps a marker for early detection. When DNA lesions are left unrepaired they can promote accumulation of mutations that facilitate the process of carcinogenesis. Micronutrients may act directly on the genome to prevent mutations, or indirectly as enzyme cofactors in cellular processes that modulate transformation (Hanahan and Weinberg, 2000; Sjoblom et al., 2006). By yet incompletely defined mechanisms, micronutrients at levels higher than nutritional requirements may also activate DNA damage response or senescence, which are processes that are recognised to eliminate cancer cells or limit the progression of precancerous cells (Gorgoulis et al., 2005; Bartkova et al., 2005, 2006). The essential microminerals copper, iron, selenium and zinc play important roles in genome stability. In particular, these microminerals have significant impact on oxidative DNA damage and the corresponding repair pathways.
Micronutrient intakes below recommended levels are known to be unusually widespread in poor countries, though also some segments of the population in economically advanced nations such as the United States, especially among the poor, children, adolescents (Anetor, 2009; Ames, 2010). It has been hypothesised that two of the many insidious but measurable consequences of moderate micronutrient inadequacy are increased DNA damage (precursor of cancer) and mitochondria decay which can cause mutagenic oxidant release also involved in future carcinogenesis. Studies indicate that sensitive assays targeted at these end points have a high probability of detecting changes in individuals with micronutrient deficiencies(Ames, 2010) This again appears instructive to scientists and technologists in the biomedical engineering field.

8. Technology and chemical carcinogenesis

Many technological advances have allowed conceptual ideas to be experimentally tested, including the sensitive detection of chemical carcinogens by high-pressure liquid chromatography (Esaka, et al., 2003) and mass spectrometry (Sigh and Farmer,2006), detection of DNA adducts by postlabeling (Randerath et al, 1981) and by specific antibodies (Poirier et al., 1977), transcriptional profiling by arrays (Kallioniemi et al., 1992, Schena et al., 1995), and quantitation of mutagenicity of carcinogens using bacterial genetics (Ames et al., 1973). The testing of certain concepts in chemical carcinogenesis awaited the development of new technologies. For example, the concept of somatic mutations in cancer preceded by 40 years the establishment of DNA as the genetic material and by 67 years the development of DNA sequencing methods that directly showed clonal mutations in human cancer cells. Also, the mutator phenotype hypothesis formulated in 1974 has been only

recently experimentally verified. The list below shows some commonly employed analytical techniques requiring the attention of biomedical engineering and technology.
Some analytical areas that may be particularly relevant in chemical carcinogenesis will include:

- 32P-post labelling
- Fluorescent-based techniques
- Immunoassay-based techniques
- Electrochemical detectors
- Electron microscopy
- High performance liquid chromatography/ Ultra high performance liquid chromatography
- Comet (Single cell gel electrophoresis), imaging system
- Mass spectrometry
- Atomic absorption spectrophotometry (AAS)
- Inductively coupled plasma- mass spectrometry (ICP-MS)
- Advanced spectrophotometry
- DNA microarray systems

The latter is particularly promising as it enables the simultaneous measurement of transcription of thousands of genes using microchips containing thousands of probes of complementary DNA (cDNA) immobilized in predetermined array. But suffers the caveat of being very expensive especially for the developing countries that appear to be mostly in need of it currently.

9. Early studies in chemical carcinogenesis and risk factors

Early in the field of chemical carcinogenesis, investigators recognized that perturbation of the normal microenvironment by physical means, such as wounding of mouse skin or partial hepatectomy in rodents (Hennings and Boutwell, 1970; Fausto etal, 2006) or chemical agents, such as exposure of the mouse skin to certain phorbol esters (Berenblum, 1941), can drive clonal expansion of the initiated cells toward cancer. In the second stage, tumor promotion results in proliferation of the initiated cells to a greater extent than normal cells and enhances the probability of additional genetic damage, including endogenous mutations that accumulate in the expanding population. This classic view of two-stage carcinogenesis (Berenblum, 1941) has been conceptually important but also an oversimplification of the increasing understanding of the multiplicity of biological processes that are deregulated in cancer. In addition, an active debate continues on the relative contribution of procarcinogenic endogenous mechanisms—for example, free-radical–induced DNA damage (Halliwell and Aruoma, 1991), DNA depurination (Lindahl and Nyberg, 1972), DNA polymerase infidelity (Loeb et al, 1974), and deamination of 5-methylycytosine (Lindahl and Nyberg, 1974)—compared with exposure to exogenous environmental carcinogens (Ames et al, 1973).
The enhancement of carcinogens by epigenetic mechanisms such as halogenated organic chemicals and phytoestrogens (Martin et al, 2007), as well as the extrapolation of results from animal bioassays for identifying carcinogens to human cancer risk assessment, are also difficult to quantify (Swenberg et al., 1998). As discussed below, this debate is not merely an academic event, in that societal and regulatory decisions critical to public health are at issue. The identification of chemical carcinogens in the environment and occupational settings

[benzo (*a*) pyrene and tobacco-specific nitrosamines in cigarette smoke, aflatoxin B_1 (AFB_1), residues from fossil fuel, vinyl chloride, pesticides and benzene] has led to regulations that have reduced the incidence of cancer. Further reduction or near total elimination may be achieved by sensitive instruments that enable early detection of up- stream changes that may culminate in cancer. This needless to say has heavy reliance on biomedical engineering.

9.1 Risk factors and early detection: role for micronutrient deficiency and oxidative stress

The risk of contracting cancer generally increases as the population grows older; this has been reported to be directly proportional to the number of years raised to the fourth power (Tolonen, 1990). This may be modified in the case of chemical carcinogenesis to include dose of chemicals or environmental agent to which the population is exposed and the stoichiometric bioavailability of protective factors such as the micronutrients. In animal models, such as the mice, the life-span of the models has been increased and cancer prevented by calorie restriction (reducing oxygen intermediates) and feeding them antioxidants. This suggests that excess calorie and antioxidant deficit (oxidative stress) are risk factors that may enhance the carcinogenic process. The natural dietary antioxidants, selenium, zinc, vitamins A, C, and E plus β-carotene protect against free radicals, lipid peroxidation (Tolonen, 1990) and thus the risk of chemical carcinogenesis. Ames (1983) has greatly emphasised the role of antioxidants largely derived from micronutrients as anticarcinogenesis. Vitamin C for instance is well known to counteract carcinogenic nitrous amine in the stomach. Urban population are more exposed to the risk of cancer than rural dwellers. This perhaps can be explained by the probability that the rural population is exposed to fewer carcinogens present in the environment.

Additionally, there is the often neglected element of greater host resistance in that rural populations are more likely to consume diet replete with antioxidant micronutrients some of which will also enhance the immune system. This is important in that its contact with carcinogens either in the diet or environment is inevitable. Thus it may be possible for us to avoid the most prominent risk factors the most pragmatic option appears to be reinforcing host resistance .This may be enhanced by the use of biomarkers. Biomarkers are playing an increasing role in the assessment of human exposure to hazardous environmental pollutants or chemicals and in risk assessment to these compounds. Biomarkers may be applied at any stage in the toxicological process, ranging from measurement of the external dose as an indicator of exposure to determine altered structure and function of cells as a marker of effect- carcinogenesis. Genetic carcinogens interact with nucleic acids to produce adducts, measurement of which is an indicator of the dose of active material which has reached the cells in question, termed biologically active dose (BAD), in the individual. This consequently incorporates the inter-individual variation in absorption, metabolism, and excretion of the compound which may affect risk assessment.

10. DNA repair: Introduction

To maintain the genomes of organisms, they have evolved a network of DNA repair pathways to excise altered residues from DNA. A major consideration is the relative contribution of environmental and endogenous DNA damage to carcinogenesis. DNA damage by environmental agents would have to be extensive and exceed that produced by normal endogenous reactive chemicals to be a major contributor to mutations and cancer.

This consideration underlines the difficulty in extrapolating risk of exposure to that which would occur at very low doses of carcinogens

10.1 DNA repair and role of micronutrients as biomarkers of susceptibility to DNA damage

Very many factors including nutritional factors have been shown to delay the carcinogenic process. Thus this can be exploited to reverse, delay or prevent the carcinogenic process. Maintenance of genome stability is of fundamental importance for counteracting carcinogenesis. Many human genome instability syndromes exhibit a predisposition to cancer. An increasing body of epidemiological evidence has suggested a link between nutrient status and risk of cancer. Populations in developing countries that are deficient in these protective micronutrients (WHO, 2002; Ames, 2010) and are increasingly exposed to chemicals owing to progressive or rapid industrialization are thus at increased risk (Anetor et al., 2008). Based on public data from the healthy people 2010 project, it is estimated that up to 80% of colon and prostate cancers may be influenced by diet, nutrition and life styles. As earlier indicated, it has been proposed that DNA damage induced by dietary micronutrient deficiency accounts for one-third of preventable cancers. Because micronutrient deficiencies can induce DNA damage in forms similar to those induced by ionizing radiation and reactive oxygen species (ROS), it has been suggested that oxidative stress and associated DNA breaks are critical targets for nutritional control of carcinogenesis. If left unrepaired, DNA lesions can promote accumulation of mutations that facilitate the process of carcinogenesis.

Micronutrients may act directly on the genome to prevent mutations, or indirectly as enzyme cofactors in cellular processes that modulate transformation. Thus micronutrient status may serve as biomarkers of risk of carcinogenesis. For instance low selenium status is a biomarker of risk of many cancers including cancer of the prostate. This should be particularly appealing to industrializing developing countries. Human cells possess an armamentarium of mechanisms for DNA repair that counter the extensiveness of DNA damage caused both by endogenous and environmental chemicals. These mechanisms include base excision repair (BER) that removes products of alkylation and oxidation (Duncan et al, 1976; Roth and Samson, 2002; Gersson, 2002); nucleotide excision repair (NER) that excises oligonucleotide segments containing larger adducts (Setlow and Carrier, 1963); mismatch repair that scans DNA immediately after polymerization for misincorporation by DNA polymerases (Modrich, 1991); and oxidative demethylation (Sedgwick, 2004), transcription-coupled repair (TCR) that preferentially repairs lesions that block transcription (Hanawalt, 1994); double-strand break repair and recombination that avoids errors by copying the opposite DNA strand (Friedberg et al, 2005); as well as mechanisms for the repair of cross-links between strands (Kuraoka et al, 2000; Zheng et al, 2005) that yet need to be established. Micronutrients deficiency disorder may inhibit DNA repair, thus acting as risk factors. Determinations of the levels of micronutrients may therefore serve as biomarker of susceptibility to DNA damage using the various instruments provided by biomedical engineering. Micronutrient deficiency for instance is inversely correlated with the level of 8-hydrodeoxyguanosine (8-OHdG), a marker of oxidative DNA damage, which is mutagenic and has to be removed by protective enzymes such as the human oxo-guanine DNA glycosylase (hOGG1).

Most DNA lesions are subject to repair by more than one pathway. As a result, only a minute fraction of DNA lesions which escapes correction are present at the time of DNA

replication and can direct the incorporation of noncomplementary nucleotides resulting in mutation. Unrepaired DNA lesions initiate mutagenesis by stalling DNA replication forks or are copied over by error-prone *trans*-lesion DNA polymerases (McCulloch and Kunkel, 2008). Alternatively, incomplete DNA repair can result in the accumulation of mutations and mutagenic lesions, such as abasic sites (Loeb, 1985). Maintenance of genome stability is crucial for avoiding carcinogenesis. A number of human cancers display a range of chromosomal abnormalities; a characteristic now termed genome instability. The relationship between cancer and genome instability is well recognized, but the causes of genome instability in the evolution of human cancers is incompletely elucidated. The DNA damage response safeguards the integrity of the genome by detecting alterations, halting cell cycle progression and repairing damaged DNA. Zinc which plays a role in all the phases of cell cycle when deficient can be critical. (Anetor et al, 2008) Cells with defective DNA damage responses are characterized by high level of genome instability (Cheng, 2009).

It is known that in particular, cells in s-phase are vulnerable to agents, such as chemicals in the environment that cause DNA damage and induce DNA replication fork arrest. Since such events can adversely affect genomic stability, cells have evolved S-phase DNA response cascades, including checkpoint responses and DNA repair mechanisms, to fix DNA damage (Bartek et al., 2004). In response to DNA damage, check points are activated that coordinate DNA damage signaling, cell cycle arrest and DNA repair. Cells have developed elaborate systems to repair varieties of DNA damage. Abundant evidence has linked defects in DNA repair to carcinogenesis. As a way of avoiding mutagenic events, the DNA base excision repair (BER) pathway copes with oxidatively modified DNA (Xu et al., 1997; Kungland et al., 1999), and nucleotide excision repair can deal with bulky DNA adducts including DNA cross-links (Cleaver, 2005). It is noteworthy that micronutrient deficiency significantly affects DNA damage repair. Zinc (Zn) deficiency is common in children and adults (WHO, 2002; Moshfegh et al., 2005). Human cell culture studies demonstrating severe Zn deficiency causes complex IV deficiency and the release of oxidants, resulting in significant oxidative DNA damage (Ho and Ames, 2002). Zinc deficiency has also been reported to cause chromosome breaks in rats (Bell et al, 1975) which has been associated with cancer in both animal models and humans (Fong et al., 2005).

These reports strengthen the significant effect of micronutrient deficiency on DNA damage repair and by extrapolation on risk of carcinogenesis particularly chemical carcinogenesis in populations exposed to chemicals. Zinc deficiency in human cells has also been shown to inactivate Zn-containing proteins such as the tumor suppressor protein, p53 which plays a significant role in genome protection (Lane, 1992) and the DNA base excision repair enzyme,apyrimidinic/apurinic endonuclease, with a resulting synergistic effect on genetic damage (Ho and Ames, 2002;Ho Courtemanche and Ames, 2003).

11. Integrative cell biology and chemical carcinogenesis

Damage to DNA by chemical carcinogens activates checkpoint signaling pathways leading to cell cycle arrest and allows time for DNA repair processes (Sweasy et al, 2006). In the absence of repair, cells can use special DNA polymerases that copy past DNA adducts (Masutani et al., 2000) or undergo apoptosis by signaling the recruitment of immunologic and inflammatory host defense mechanisms. The demonstration that each methylcholanthrene-induced tumor has a unique antigenic signature provided one of the earliest glimpses into the stochastic nature of cellular responses to carcinogens. The

immunologic and inflammatory responses facilitate not only engulfment and clearance of damaged cells but also the resulting generation of reactive oxygen (Klebanoff, 1988) and nitrogen radicals (Ohshima and Batsch, 1994) that further damage cellular DNA.

12. Chemical carcinogens and induced somatic mutations as biomarkers in molecular epidemiology

Extensive experience of laboratory research in chemical carcinogenesis has provided a solid foundation for the analysis of chemical-specific macromolecular adducts and related somatic mutations in humans as biomarkers of carcinogen exposure. A paradigm for validating causal relationships between biomarkers of carcinogens exposure and a cancer risk biomarker is shown in a number of observations (Wogan et al, 2005). The metabolite, AFB_1, a fungal toxin, is a prototypical example of an environmental chemical carcinogen that has been validated using this strategy. Benzo (a) pyrene, a polycyclic aromatic hydrocarbon 4-aminobiphenyl (Vineis and Pirastu, 1997), an aromatic amine dye, and 4-(N-methyl-N-nitrosamino)-1-(3-pyridyl)-1-butanone, a tobacco-specific N-nitrosamine (Hetch, 1999), are other key examples. The prevalence of Aflatoxin B1 in developing countries makes host resistance mechanism based on micronutrients of great import to reduction of risk of chemical carcinogenesis.

13. Impact of new technologies or analytical techniques and biomedical engineering

Recent advances in molecular methodologies are phenomenal, and they increasingly are being applied to understanding the interaction of chemical carcinogens with cellular constituents and metabolism. Cloning of DNA has facilitated the identification of specific genes mutated in human cancers. Chemical methods, including mass spectrometry, allow us to measure carcinogen alteration with unprecedented sensitivity and specificity, particularly the ultra high performance liquid chromatography (UHPLC) coupled to MS. Mass spectrometry is being coupled with many other site-specific techniques to study mutagenesis; to define how specific alterations in DNA produce cognate mutations. Sequencing of the human genome and the identification of DNA restriction enzymes opens up the field of molecular epidemiology, focusing in part on individual susceptibility to carcinogens.

A very useful technique in cancer studies is the single cell protein electrophoresis (COMET ASSAY). This assay is the only direct method for the detection of DNA damage in cells. It is used in cancer research, in genotoxicity studies on environmental mutagens, and for screening compounds for cancer therapeutics.

DNA microarray technology is a powerful tool that allows the activity of several genes to be monitored simultaneously. DNA microarray has been especially useful for detecting genes that respond to a specific chemical or physical signal in the same way. A DNA microarray or DNA chip consists of a solid surface, usually glass, to which DNA fragments are attached. The copies of each kind of fragments are attached to the glass surface at a specific site to regular pattern or array. DNA fragments attached to the chip act as probes that can hybridize with complimentary DNA or RNA molecules (targets) in solution. DNA microarray technology has been used to study a wide variety of gene expression problems such as tissue specific, cell cycle specific, and tumor- specific gene activation and repression.

Once a similar pattern expression profile has been established for a group of genes, it seems reasonable to assume that the profile is at least partly caused by similar transcription regions. Therefore, if information is available about a regulatory region in one gene within this group, it may provide clues to the regulatory regions of other members of the group as well as to the protein factors that activate or inhibit gene expression. The initial stimulus may be a given carcinogen. Array technology facilitates analysis of carcinogen-induced alterations in the expression of both protein coding and noncoding genes. These are all areas where biomedical engineering is expected to play a pivotal role in risk identification and early detection. On the horizon are techniques that can measure single molecules of carcinogens in cells, random mutations in individual cells, analysis of the dynamics of how molecules exist and work, and bioinformatics and genetic maps to delineate complex interacting functional pathways in cells. Underlying this progress in understanding chemical carcinogenesis is a cascade of advances in molecular biology that makes it feasible to quantify DNA damage by chemical agents, mutations, and changes in gene expression.

This calls for very intimate collaboration between biotechnology and biomedical engineering, a partnership that promises to be very rewarding in the fight against chemical carcinogenesis. Determining the structure of DNA, DNA sequencing, and the PCR revolutionized cell biology, including carcinogenesis. Advances in detection of DNA damage, including postlabeling of DNA (Randerath et al, 1981), immunoassays (Poirier et al, 1977) and mass spectrometry as earlier discussed (Singh and Farmer, 2006) have allowed the detection of a single altered base in 10^9 nucleotides using human nuclear DNA. This technology can be extended to analyze DNA or RNA in a single cell (Klein, 2005). Advances in cell biology, including array technology (Schena et al, 1995) and proteomics (Anderson et al, 1984; Aebersold et al, 1987), make it feasible to assess global changes in RNA and protein expression during carcinogenesis. Together, these technologies underlie systems biology, making it increasingly feasible to map biochemical pathways in cancer cells from DNA, to RNA, to proteins, to function. This again calls for greater involvement of the biomedical engineering field.

The ultimate application of techniques of biomedical engineering in the field of chemical carcinogenesis holds great promise, but faces several formidable challenges requiring ingenuity in matching technology with a social obligation to ensure that those most affected can afford its dividend to combat the menace of chemical carcinogenesis. This calls for sensitive methods for the early detection. The complex interplay among these and the great promise they hold for human health, particularly in the rapidly industrializing developing countries has not been adequately addressed. This contribution largely sees this as needing to be addressed- carcinogenesis, integrating chemical exposure, nutritional; mainly micronutrient modulation and the yawning gap biomedical engineering should fill in non-invasive applications. Although the field of biomedical engineering as regards cancer studies is still relatively in its early stages and will be a long-term effort and the magnitude of the task far greater than the physical resources and intellectual capacity currently available, the challenge is to focus on sensitive, specific or selective, cost effective and efficient techniques with dereliction for resource poor rapidly industrializing developing countries that appear to bear a greater brunt of the increasing chemical exposure and attendant carcinogenic risk.

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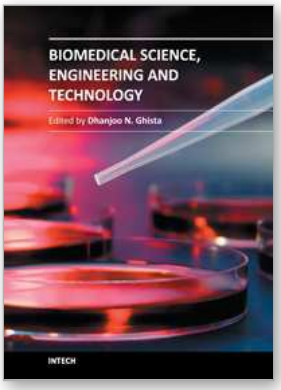

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This innovative book integrates the disciplines of biomedical science, biomedical engineering, biotechnology, physiological engineering, and hospital management technology. Herein, Biomedical science covers topics on disease pathways, models and treatment mechanisms, and the roles of red palm oil and phytomedicinal plants in reducing HIV and diabetes complications by enhancing antioxidant activity. Biomedical engineering coves topics of biomaterials (biodegradable polymers and magnetic nanomaterials), coronary stents, contact lenses, modelling of flows through tubes of varying cross-section, heart rate variability analysis of diabetic neuropathy, and EEG analysis in brain function assessment. Biotechnology covers the topics of hydrophobic interaction chromatography, protein scaffolds engineering, liposomes for construction of vaccines, induced pluripotent stem cells to fix genetic diseases by regenerative approaches, polymeric drug conjugates for improving the efficacy of anticancer drugs, and genetic modification of animals for agricultural use. Physiological engineering deals with mathematical modelling of physiological (cardiac, lung ventilation, glucose regulation) systems and formulation of indices for medical assessment (such as cardiac contractility, lung disease status, and diabetes risk). Finally, Hospital management science and technology involves the application of both biomedical engineering and industrial engineering for cost-effective operation of a hospital.

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