CRC

# HANDBOOK of ENVIRONMENTAL GENOTOXICOLOGY

## Volume II
## Age and Genotoxicology

Eugene Sawicki

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# CRC Handbook of Environmental Genotoxicology

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## Age and Genotoxicology

Editor

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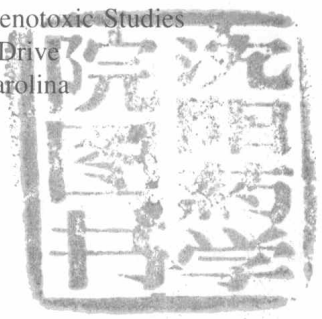


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# PREFACE

The volumes in this series are intended for anyone who is interested in the genotoxic effects of chemicals, radiation, and other physical agents on human beings. Although animal research has been discussed, the main emphasis has been on human studies. Cellular and animal research investigations have been utilized whenever they shed some light on a human problem. The main thrust has been on human genotoxicology, whether it involved (1) germ cell mutations of the point or chromosomal type in our ancestors or in the present generation or (2) somatic cell mutations of the point or chromosomal type in the somatic cells of the body, the embryo or the brain (and especially the neurons).

The problems of human carcinogenesis and the carcinogens (industrial, nuclear, life style, and iatrogenic) to which we are exposed have been discussed at some length.

The series on Environmental Genotoxicology will consist of three volumes. In Volume I some examples of genotoxicants and environmental genotoxicology have been presented. In this case a small representative slice of the pie has been provided. Each volume is incomplete at one level in that each part is necessary to a thorough treatment of the field as it applies to human beings. But at another level the sections in each volume are complete in a concise way and can stand by themselves, in that they contain a pertinent discussion and references.

Volume II continues the discussion on environmental genotoxicology, but is concerned mainly with the role of age in the physiological effects of environmental genotoxicants on human beings. Many of the terms used in both volumes have been defined in this volume; examples and discussions have also been presented so as to enhance and clarify the definitions. Volume III continues the dialogue but is mainly concerned with the role of age in cancer.

A large amount of data has also been presented on the problems interfering with the abolishment of our genotoxic diseases. Of these, conflict of interest seems to be the most important obstacle in obtaining a workable consensus necessary to the solution of our genotoxic problems. We have given many examples of the genotoxic damage caused by those who profited from the exposure of populations to carcinomutagens. A prime example is the golden leaf, tobacco. We have pointed out that the problems of cancer, the mutations and aging will not be solved as long as those who expose individuals to genotoxicants also investigate the effects of the exposure. This applies to industry, to the medical profession and to nuclear power, whether it be for energy production or for weaponry. These are conflicts of interest that interfere seriously with our attempts to solve the problems of cancer, the mutations, and aging.

These conflicts of interest lead to the next premise. There is tremendous difficulty and conflict in attempting to derive meaning from extrapolation studies utilizing mammals and in recent years a variety of nonmammalian species. Much of this controversial extrapolation can be substituted by human studies since there is a tremendous amount of human experimentation that is either not investigated or is investigated inadequately, usually because of conflict of interest interference, indifference or ignorance. It is to the benefit of all of us (and if it is too late for us, it is to our children's benefit) to solve our conflict of interest and extrapolation problems.

**Gene Sawicki**
April 1983
Raleigh, North Carolina

I saw Good and Evil battling; their
every encounter shook the earth around me.
With despair I saw Evil winning, but
then Good acquired status, influence
and money. The battle began to turn,
and I knew Good would win. And I
shivered with fright at the future that
awaited us.

**Arrl Elvs — 1982**

# THE EDITOR

**Dr. Eugene Sawicki** has had a widely varied experience in clinical chemistry, cancer research, and environmental analysis. He has received a B.S., magna cum laude in chemistry, and a M.S. in organic chemistry from the University of Cincinnati, and a Ph.D. in biochemical oncology from the University of Florida, Gainesville. He has spent 4 years in clinical chemistry, 4 years in cancer research, and 22 years in the EPA as one of the country's foremost pioneers in developing, evaluating, and applying methods of analysis for carcinogens, mutagens, allergens, and other pollutants in emission sources, industrial and outdoor atmospheres, and other ambient environments. He has directed or been in the forefront in the development and application of numerous analytical techniques (including thin-layer chromatography, high performance liquid chromatography, gas-liquid chromatography, electrophoresis, ion chromatography, mass spectrometry, ultraviolet, visible and infrared absorption spectrophotometry, spectrophotofluorimetry, and spectrophotophosphorimetry to the analysis of environmental pollutants. A large number of genotoxicant screening methods have been developed or utilized under his direction. He has been a Chairman of the Subcommittee on Hydrocarbons, Organic Airborne Particulates, and Industrial Carcinogens of the Intersociety Committee. Dr. Sawicki has been or is a member of the Editorial Advisory Boards of *Analytical Chemistry, Microchemical Journal, Analytical Letters, Environmental Analytical Chemistry, Toxicology and Environmental Reviews,* etc. He has been the author of over 200 scientific papers published in organic chemical, analytical, environmental, and medical journals and is the author of nine books. He has presented papers all over the world at chemical, analytical, environmental, biological, and medical symposia. He has been a consultant to the National Cancer Institute on their contracts concerned with environmental carcinogenesis. He was on the Cancer Hazards Ranking and Information System Advisory Committee and also contributed to the Carcinogen Metabolism and Toxicology Segment Advisory Group.

He has also consulted and contributed to several publications of the International Agency for Research against Cancer. He is a member of Phi Beta Kappa and has received government superior service awards in 1959 and 1960, the "Cincinnati Chemist of the Year Award" in 1968, the Detroit Anachem Award in 1968, the Benedetti-Pichler Award from the Microchemical Society in 1974, the U.S. Government Bronze Medal in 1978, and the Distinguished Career Award from the U.S. Government in 1979.

He has an intense interest in exploration, poetry, literature, photography, environmental pollution, environmental analytical chemistry, mutagenesis, carcinogenesis, chromosome aberrations, evolution, aging, and other aspects of genotoxicology.

DEDICATION

To my wife,
without whom these volumes
would not have been possible.

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## DEFINITIONS

**Allele (allelomorph)** — an alternative form of a gene occupying the same locus on homologous chromosomes. Alleles segregate at meiosis, and an individual normally receives only one of each pair of alleles from each parent. For further details see Singleton and Sainsbury.[942]

**Aneuploidy** — a karyotypic abnormality resulting from extra chromosomes or absence of chromosomes, so that the karyotype is not characteristic of cells of the species and is neither haploid nor an exact multiple thereof.

**Autosomal dominant** — used in reference to a syndrome wherein the damaged gene of the autosome is dominant as compared to the other gene in the diploid cells, so that the damaged gene of the pair is expressed. Examples of such syndromes are achondroplasia, dystrophia myotonia, epiloia, Marfan's syndrome, and neurofibromatosis.

**Autosomal recessive** — used in reference to a syndrome wherein the damaged gene of the autosome is recessive as compared to the other gene in the diploid cells, so that the damaged gene of the pair is not expressed. Examples of such syndromes are androgenital syndrome, albinism, fibrocystic disease, galactosemia, mucopolysaccharidoses, phenylketonuria, and Tay Sachs. See for example Edwards.[228]

**Autosome** — any chromosome other than the sex chromosome. In males and females 22 of the 23 pairs of autosomes are the same. The other pair are X chromosomes in the female and an X and Y chromosome in the male.

**Back mutation** — a mutation which reverses the effect of a forward mutation by restoring the original nucleotide sequence. This type of mutation has been utilized by Ames and Yanofsky[12] and many other researchers to detect chemical mutagens in the environment, in biological fluids and tissues, and in foods.

**Banding** — the technique of staining chromosomes in a characteristic pattern of cross bands, thus allowing individual identification of each chromosome pair. Bands are defined as both the deep and light staining segments and are numbered from the centromere. The more the chromosome is stretched the more detail is obtained. Two of the most popular banding techniques are Giemsa banding (G banding) and quinacrine fluorescence banding (Q banding).

**Barr body** — a mass of stained chromatin in the nucleus of resting cells resulting from inactivation of an X-chromosome. A cell ordinarily contains a number of Barr bodies equal to the number of X-chromosomes minus one. For example, females with trisomy X, tetrasomy X, and pentasomy X show about 10 to 20% Barr bodies (two, three, and four, respectively) in the buccal smear cells. See Yunis et al.[1117] for further details.

Valentine has discussed the Barr body.[1048] In the nucleus of any tissue of a human female a tiny darkly-staining body is found alongside the nuclear membrane in many cells. The belief is that where two X chromosomes are present in a cell, as in the human female, one is attenuated, active, and invisible as it goes about its transmission of the genetic code. The other is largely but not entirely condensed and mainly inactive genetically. Valentine has concluded it is this largely unrequired X that is visible as the Barr body.[1048]

**Base pairing** — in the DNA double helix, the hydrogen bonding of adenine with thymine and of guanine with cytosine, while in RNA adenine forms a hydrogen bond with uracil

and guanine with cytosine. This specific base pairing is fundamental to DNA replication and to its transcription into RNA for protein synthesis. Any change in this system would result in mutation.

**Benign tumor** — an abnormally increased growth of tissue which is encapsulated, highly differentiated, noninvasive, and characterized by rare mitoses, slow growth, little or no anaplasia, and no metastases. The spread of these tumors is observed as a simple increase in tumor size until some natural barrier is reached. See Davies[198] and Pitot.[793]

**Biological clocks** — mechanisms that allow expression of genes at periodic intervals and even sometimes cause termination of expression. Thus, the life and death of a 107-year-old person could be considered as an almost pure example of the phenomenon of aging→senescence→death, at which stage the preordained clock had run out.

**Carbon-14** — a radioactive carbon isotope emitting a weak beta particle (electron). Its half-life is 5730 years. According to Gofman, the dose from radionuclides produced on earth from cosmic radiations is largely the dose from carbon-14, about 1.3 mrad per year.[317]

**Cancer** — a group of diseases that are characterized by uncontrolled cellular growth. Some investigators believe that it is one disease that affects different cells and tissues. Other investigators believe not enough is known to even define the term. Pitot has stated that cancer has become a layman's term which is utilized almost exclusively to indicate a process which has the biological characteristics of a malignant neoplasm.[793]

**Carcinogen** — any agent that increases the probability of induction of benign or malignant tumors in man or animals with the result being (1) an increase in the tumor incidence in a given population, (2) an increase in the number of tumors per individual, (3) a reduction in the latent period of tumor induction, or (4) any combination of the above effects. This could be a chemical, a virus, or a physical agent such as radiation, a burn, or a surgical scar. For further details see Bralow and Weisburger[105] and Epstein.[242]

**Carcinogen, human** — as above. The evidence would include (1) neoplastic response directly related to exposure (both duration and dose), (2) incidence and mortality differences related to occupational exposure, (3) incidence and mortality differences between geographic regions related to different exposures rather than genetic differences and/or altered incidence in migrant populations, (4) time trends in incidence or mortality related to either the introduction or removal of a specific agent from the environment, (5) case control studies, and (6) the results of retrospective-prospective and prospective studies of the consequences of human exposure. This is attributed to NCI by Gibney.[310]

**Carcinogenesis** — (derived from the Latin "carcinus", the crab, and "genere", to make, to create). It is essentially the generation of benign and malignant neoplasia in the broadest possible sense, including the generation of sarcomata, lymphoma, and leukemia. Present belief is that it is composed of an initiating process responsible for the conversion of normal into latent tumor cells, a promoting process wherein these latent tumor cells are made to develop into actual tumors, and a progression stage wherein the cancer cells invade adjacent tissue and also metastasize to distant tissue.

**Carcinogenesis, viral** — Tumor induction by RNA oncogenic viruses (retroviruses) can be explained by any one of the following hypotheses: (1) the oncogene-virogene hypothesis, (2) the protovirus hypothesis, and (3) the exogenous virus hypothesis. For further details see Burney et al.,[122] Bishop,[79] and Fiennes.[265]

**Carcinoma** — cancer of the epithelial cells (i.e., those cells covering internal and external surfaces of the body; malignant neoplasms arising from tissues derived from embryonic ecto- or endoderm). Peto has reported that in the developed countries, the cells of origin of fatal malignant tumors are distributed approximately as follows: (1) 20% of fatal malignant tumors are carcinomas arising from the sex-specific epithelial cells, (2) 70% are carcinomas arising from the other epithelial cells, (3) 10%, including all the leukemias and sarcomas, arise from nonepithelial cells and are therefore not carcinomas. Peto has stated that 90% of malignant human cancers are carcinomas and has suggested that fatal neoplasms could be subdivided into (1) carcinomas of sex-specific organs, (2) other carcinomas, (3) tumors (excluding plaques) of nonepithelial cells, and (4) atherosclerotic plaques, assuming these plaques are benign tumors.[788]

**Carcinosarcoma** — a highly malignant tumor having the appearance of both a carcinoma and a sarcoma. An example is carcinosarcoma of the endometrium which is an uncommon tumor of the endometrial stroma and which may metastasize as a carcinoma, a sarcoma, or a combination of both, according to Norris et al.[752]

**Carrier** — an individual heterozygous for a recessive gene. Such a person may be clinically normal, but with appropriate mating can produce offspring with the homozygous condition.

**Catalase** — (hydrogen peroxide: hydrogen peroxide oxidoreductase, EC 1.11.1.6) a protohaem-containing enzyme which catalyzes the reaction:

$$2H_2O_2 \rightarrow 2H_2O + O_2$$

The marker enzyme of the cell organelle, peroxisome, a hemoprotein which decomposes hydrogen peroxide catalytically as well as peroxidatically. For further details see Deisseroth and Dounce,[204] Fridovich,[292] Halliwell,[365] and Sies.[937]

**Cell** — the fundamental unit of life and the smallest body capable of independent reproduction. The cell is the basic structural and functional unit of all living matter and consists of a multimembraned system, compartmentalized into specific functional areas or organelles with discrete but completely interrelated and coordinated roles. In terms of genotoxic effects, cells can be divided into somatic, germinal, embryonal, and neuronal. According to Leblond, cell populations can be classified as static (e.g., neurons), expanding (e.g., parenchymal cells of liver and kidney, muscle fibers, etc.), renewing (e.g., cells of epidermis, intestinal epithelium, thymus, etc.), and neoplastic, where proliferation of the cells and the cell progeny tend to continue indefinitely.[572]

Peto[788] has divided the cell types of the human body into three groups: (1) sex-specific epithelial cells (e.g., the epithelial cells of the breast, cervix, vagina, endometrium, ovary, prostate, testis, vulva, penis, scrotum, etc.), (2) other epithelial cells (e.g., the epithelial cells of parts common to both male and female, including bladder and kidney), and (3) nonepithelial cells (e.g., neural cells, germ-line cells, melanocytes, reticuloendothelial cells, blood vessels, bones, muscles, and other connective and soft tissues, together with any cells that have never differentiated into epithelium, such as those cells which give rise to the various teratomas and blastomas).

The properties of a cell can be seen from Lehninger's report on the *Escherichia coli* cell.[578] He reported that this cell was about $1 \times 1 \times 3$ μm in size, had a volume of 2.25 $\mu m^3$, a total weight of $10 \times 10^{-13}$ g, a dry weight of $2.5 \times 10^{-3}$ g, contained about four molecules

of DNA (mol wt ≈2 billion), 15,000 molecules of RNA (mol wt ≈1,000,000), 39,000 molecules of polysaccharides (mol wt ~200,000), 1,700,000 molecules of protein (mol wt ~60,000) and 15,000,000 molecules of lipids (mol wt ~1000). For further details see Rieger et al.[840]

**Cell differentiation** — the process by which specialized cells, tissues, and organs are formed during the development of the individual from the fertilized ovum. Britten and Davidson[107] have discussed the belief that cell differentiation is based on the regulation of gene activity, so that for each state of differentiation a certain set of genes is active in transcription and other genes are inactive. For further details see Malamud,[619] Levenson and Housman,[582] and McKinnell et al.[658]

**Cell proliferation** — the reproduction or multiplication of similar cells. Frei[291] has suggested that increased cell proliferation may affect tumor induction by (1) alteration of the balance between DNA repair and DNA replication, and (2) chronic repeated cell proliferation. Columbano et al.[166] have shown that cell proliferation was required for the induction of presumptive preneoplastic lesions in rat liver, which falls in line with the report of Cayama et al.[140] that initiation of chemical carcinogenesis requires cell proliferation. Player et al.[796] have reported that lipid peroxidation may be involved in the control of cell proliferation. Rowe et al.[860] have reported that skin fibroblast cultures from patients with diabetes exhibit abnormalities in cell proliferation. The importance of cell proliferation is stressed by Martin's report of the various types of cell proliferations that accompany a variety of age-related disorders such as AS, benign prostatic hypertrophy, osteoarthritis, senile lentigo (liver spots), etc.[627]

**Central dogma** — the basic relationship between DNA, RNA, and protein: DNA serves as a template for both its own duplication and the synthesis of RNA, and RNA, in turn, is the template in protein synthesis.

**Chromatid** — one of two parallel daughter strands of chromosome held together by the centromere, becoming visible between early prophase and metaphase of mitosis and between diplotene and the second metaphase of meiosis. A single-stranded chromosome replicates during the DNA synthesis stage of the cell cycle and is then composed of two chromatids until the next mitotic division, at which phase each chromatid becomes a chromosome of a daughter cell.

**Chromatid aberration** — a category of chromosome structural changes involving one chromatid at a single locus. These changes could be gaps, breaks, exchanges, or deletions. Chromatid aberrations arise spontaneously or are induced experimentally by mutagens during and after chromosome reduplication in the interphase nuclei. Examples of these aberrations are the nonrandom patterns of intrachromosomal distribution of induced chromatid aberrations after mutagen treatment of a variety of organisms as reported by Schubert and Rieger;[909] the chromatid aberrations induced by actinomycins, adriamycin, daunomycin, and mitomycin C as reported by Vig;[1057] chromatid aberrations induced by ionizing radiation as reported by Revell;[836] the high rate of chromatid-type aberrations in PVC workers as reported by Szentesi et al;[1001] chromatid-type aberrations in subjects exposed to methylmercury through the intake of fish from contaminated waters as reported by Skerfving et al;[945] and the significant excess of chromatid and chromosome aberrations among smokers.

**Chromosomal (chromosome) aberrations** — in the broadest sense all types of changes in chromosome structure and chromosome number (see chromosomal mutations). In a more

restricted sense, these aberrations are a category of chromosome structural changes in which both chromatids of the chromosomes are involved, as opposed to chromatid and subchromatid aberrations. According to Hoffmann these gross rearrangements of the genetic material may involve the deletion of chromosomal segments, the duplication of regions of the chromosome, the inversion of the order of genes in a particular chromosomal region, or the translocation of chromosomal segments to a new location in the same or a different chromosome.[413]

In another version these aberrations are considered to consist of chromosome-type aberrations. Brogger has stated that the damage processed by the cell into break or exchange events before the S phase will appear as chromosome-type aberrations involving both chromatids in the metaphase chromosome.[110] Damage processed during or after the S phase appears as chromatid-type aberrations affecting one chromatid only.

These aberrations can also be subdivided on the basis of stability. This aspect has been discussed by Anderson and Longstaff.[17] They have emphasized that structural changes are mainly the result of breaks in the chromatid arms. Depending on the number of breaks and the way in which they may join again, a whole series of unstable structural modifications may arise that are not transmitted to successive cellular generations, such as gaps, breaks of one or both the chromatids, chromatid interchanges, acentric fragments, and ring and dicentric chromosomes. They stated that stable structural modifications that are transmissible may also arise, such as inversions, translocations and deletions.

Three examples of chromosome and chromatid aberrations that have arisen because of exposure to some genotoxicant are (1) women who have been occupationally exposed to lead (see Forni et al.[275]), (2) a variety of organisms that have been exposed to ionizing radiation, and (3) exposed cells.[639]

**Chromosomal mutation** — structural or numerical aberrations according to Kapp.[503] Others have defined it as any structural alteration in a chromosome. Examples of chromosomal mutations (according to Kapp's definition) are Down's, Klinefelter's, and Turner's syndromes.

**Chromosomal rearrangement (CR)** — any process of chromosomal alteration that produces either a change in nuclear DNA content or the physical exchange or reordering of pre-existing DNA sequences (according to Radman et al.[823]). Base substitution and frameshift are not considered mechanisms of chromosomal rearrangement. CR has been divided into three classes: (1) homologous recombination involving the processes of reciprocal recombination, gene conversion, and SCE; (2) nonhomologous recombination involving processes of physical exchange or reordering of pre-existing DNA sequences that do not depend on extensive sequence homology as, for example, reciprocal translocation, transposition, deletion, insertion, and inversion, and (3) ploidy change involving processes that result in the gain or loss of entire chromosomes, such as mitotic nondisjunction, chromosomal endoreduplication, and nuclear fusion.

**Chromosomal rearrangement theory of carcinogenesis** — the postulate of Radman et al. that carcinogens can act to induce CR by creating or revealing sites on DNA for recombination or by inducing or activating cellular systems resulting in a stimulation of recombination.[823] Previous work by Cairns[126] and by Kinsella and Radman[522,523] has discussed this possibility. Radman et al. have stated that chromosomal rearrangements may affect carcinogenesis by altering gene expression, perhaps by allowing the activation of cellular cancer genes.[823] They have reported that all carcinogens that have been thoroughly tested have been found to induce some kind of CR. They have suggested that CR is probably a step in the cancer

pathway because of (1) the association of CR with human and rodent cancers and with cancer-prone syndromes and (2) the finding that DNA from nonmalignant cells can transform other nonmalignant cells, under conditions that may involve CR.

Cairns has presented many examples of human cancers that are apparently not caused by conventional mutagens but are more likely to be the result of genetic transpositions.[126] He concluded that large CRs are usually the crucial steps in carcinogenesis, but there are exceptions in certain classes of cells where the critical changes either are not rearrangements or are on too small a scale to be detected by chromosomal banding techniques. The relationship between genes, chromosomes, and cancer has been discussed in a volume by Arrighi et al.[38] Examples of cancers with associated chromosomal rearrangements have been listed by Berger et al.[65] and by Radman et al.[823] and are given here in Table 1.

**Table 1**
**CHROMOSOME REARRANGEMENTS AND CANCER**

| Rearrangement | Disease |
|---|---|
| t(4; 11)(q21; q23) | ALL |
| t(8; 21)(q22; q22) | AML with maturation |
| t(15; 17)(?q25; ?q22) | APL |
| t(14q; 14q)(q11 or 12; q34) | AT |
| t(8; 14)(q24; q32) | Burkitt's lymphoma |
| t(2; 8)(p12; q23 or q24) | Burkitt's lymphoma |
| t(8; 22)(q24; q11) | Burkitt's lymphoma-leukemia |
| Increased ploidy | Cervical carcinoma |
| t(9; 22)(q34; q11) | CML; $Ph^1$-positive ALL + AML |
| Reciprocal 8/14 translocation | Lymphoma |
| Loss or deletion of chromosome 22 | Meningiomas |
| 13qD deletion | Retinoblastoma |

**Chromosome** — a thread-like body found in the nucleus of a cell and containing a linear sequence of genes. Chromosomes of eukaryotes and prokaryotes are essentially involved in two main activities: (1) the transmission of genetic information from cell to cell and generation to generation, and (2) the ordered release of this information to control cellular function and development.

**Chromosome number alterations** — numerical chromosomal mutations. According to Kapp numerical errors are termed aneuploidy or nondisjunction and can occur during meiosis or in the early stages of mitosis in the zygote and represent a failure of homologous chromosomes to separate during cell division.[503] The net result is cells which possess one too few chromosomes (monosomy) or those which possess one too many chromosomes.

Hoffman has pointed out that alterations in chromosome number include polyploidy in addition to aneuploidy.[413] Polyploidy involves the presence of extra complete sets of chromosomes. Examples of the results of aneuploidy in humans include trisomy 21 (Down's syndrome), X monosomy (as in most cases of Turner's syndrome), trisomy 13 (Patau syndrome), XXY syndrome (as in most cases of Klinefelter syndrome), etc.

Anderson and Longstaff have reported that variations in the number of chromosomes (aneuploidy and polyploidy) may result from endoreduplication (continued chromosome division), metaphase arrest, anaphase retardation, and nondisjunction in mitosis and meiosis.[17]

**Chronic lymphocytic leukemia (CLL)** — chronic lymphoblastic, lymphatic, lymphogenous, and lymphoid leukemia all designate a type of slowly growing leukemia characterized by an increase in apparently mature lymphocytes in the peripheral blood, lymph nodes, spleen, bone marrow, and occasionally also in such organs as the skin, lungs, and intestinal tract. It is the most commonly encountered leukemia and is a collection of closely related disorders not clearly separable. CLL is defined by Rundles and Moore as a disease associated with the persistent and usually progressive proliferation or accumulation of immunologically-defective, monoclonal B lymphocytes.[869] It is a disease of aging and occurs in an older group of individuals than other varieties of leukemia: 90% of patients with CLL are over 50 years of age, and about two thirds are over 60 years of age. CLL is a disease with a broad spectrum of apparent clinical activity ranging from benign to aggressive. There is a 2:1 predominance of males, and the risk of developing CLL if a close family member already has the disease is about 10%. For further details see Silver et al.[938] and Tartaglia.[1011]

**Chronic myelocytic leukemia (CML)** — chronic myelogenous, myeloid, or granulocytic leukemia all designate a type of slowly progressing leukemia characterized by the excessive proliferation of cells of the granulocyte series, starting in the bone marrow and then appearing in the blood and elsewhere. In typical Western populations CML comprises about 15% of all leukemias and CLL about 25%. According to Gunz, in Western populations the proportion of the acute leukemias has been rising and that of the chronic leukemias has been falling over the years.[358] The greatest incidence of CML occurs between the ages of 25 and 60 with the peak at approximately age 40. Many investigators believe that CML is clinically typified as a biphasic disease of about 3 years followed by malignant transformation and subsequent survival of about 3 months. Pedersen has suggested that the chronic phase of CML is a preleukemic condition which has a very high *a priori* probability of turning into AML (the blastic crisis).[779] On the other hand Stryckmans et al. have suggested that three different phases of CML are important in the study of the pathogenesis of the disease.[983] The phase at diagnosis and during relapse is characterized by a high leukocyte count and by a heavy infiltration of the spleen and marrow by leukemia cells. The phase of unmaintained remission is characterized by an almost normal blood picture with persistence of the Philadelphia ($Ph^1$) anomaly. The phase of blastic transformation or metamorphosis is usually irreversible and fatal.

The importance of the Philadelphia chromosome is shown by Lawler's report that the median survival for $Ph^1$-positive CML patients is 40 months, whereas the median survival for $Ph^1$-negative patients is only 8 months.[571] In excess of 85% of the patients with CML have a Philadelphia chromosome usually as the result of a translocation between a chromosome 9 and a chromosome 22.

The Philadelphia chromosome involves a deletion of chromosome number 22; the deleted material is translocated to another autosome, usually a number 9, t(9:22)(q34; q11). In excess of 85% of the patients with CML have a $Ph^1$, with approximately 75% of the patients in the acute phase possessing other abnormalities such as trisomy 19, trisomy 8, a second $Ph^1$, a missing Y chromosome, etc. Sandberg has discussed $Ph^1$ and CML extensively from the cytogenetic viewpoint.[881]

The main factor that contributes to the causation of CML is ionizing radiation and especially exposure to X-rays as shown in anonymous reports[24,25] and other reports by Gunz,[358] Sato et al.,[886] and Shimaoka.[932,933] Gunz has also reviewed the causation of CML by benzene.[358] See also Liepman.[590]

**Clastogen** — an agent capable of inducing chromosome structural changes. Examples of some human clastogens are alcohol (see Obe and Herha[760]), cadmium and lead (see Bauchinger et al.[53]), vinyl chloride (see Heath et al.[388] and Szentesi et al.[1001]), cigarette smoke (Obe and Herha[761]), etc.

**Clone** — a population of cells or organisms derived from a single cell or common ancestors by mitoses. The development of a malignant tumor or a benign growth (as postulated for the atherosclerotic plaque) has been attributed by many investigators to the selection and growth of a single clone originating in one or more mutational events. See Goldenberg and Pavia,[322] Nowell,[756] and the section on AS for further details.

**Cocarcinogen** — any agent that enhances the effect of a carcinogen; this can be by increasing the incidence of tumors and/or decreasing the latent period. Examples are asbestos and cigarette smoke in the enhancement of laryngeal carcinoma (see Shettigara and Morgan)[931] and alcohol and cigarette smoke. Schmidt and Popham have emphasized that in the development of carcinomata of the oral cavity, pharynx, larynx, and esophagus, alcohol consumption and smoking each have an independent effect, and a synergistic effect when combined.[904]

Another example of cocarcinogenic effect is the report of Keller[511] that the relative frequency of cancer of the floor of the mouth and liver was increased significantly in cancer patients with cirrhosis who also smoked and drank heavily. He concluded that his results emphasized the central roles of tobacco, alcohol, and age factors in the epidemiology of liver cirrhosis and cancer.

A third example is the report by Bross and Coombs of the early onset of oral cancer among women who drink and smoke.[112] The relative age-adjusted risks for mouth cancer among light drinkers and nonsmokers, nondrinkers and smokers, light drinkers and smokers, and heavy drinkers and smokers were 1.16, 3.22, 4.03, and 10.35, respectively. The corresponding risk values for tongue cancer by the same categories were 1.35, 2.02, 3.51, and 10.87, respectively. When the effect of age shift on the chi-square value for age-adjusted relative risks for mouth cancer was examined, women who were light drinkers and smokers were susceptible to the onset of mouth cancer 12.5 years earlier than abstainers (at the 5% probability level). Women who were heavy drinkers and smokers showed a 20-year shift in onset, even at the 1% probability level. Women who smoked but did not drink showed a 10-year shift in age of mouth cancer onset. Similar results were obtained for women with tongue cancer, except for those who smoked but did not drink; this latter group was not significantly different from abstainers. Exposure to alcohol only did not produce any clear shifts in age of cancer onset for either mouth or tongue cancer. The combined effects of smoking and drinking appear to be particularly significant in terms of the age of intraoral cancer onset.

**Cocarcinogenesis** — all forms of augmentation of tumor induction, usually brought about by concurrent exposure to the carcinogen and the cofactor, although in some cases, the cofactor operates before or after the carcinogen. This definition is essentially Berenblum's definition of the experimental situation, but modified slightly so as to fit the human situation. It is the definition we use in these volumes.

In his 1969 paper Berenblum listed seven types of modifying influences.[64] These are repeated here in Table 2.

**Table 2**
**COCARCINOGENIC EFFECTS**

| Effect | Description |
|---|---|
| Additive | Cofactor is carcinogen also |
| Synergism | Combined effects exceed summation |
| Incomplete | Either initiation or promotion |
| Preparative | Rendering target organ more responsive to carcinogenic action |
| Permissive | Affecting scope of action of carcinogen such as solubility, rate of absorption, metabolic rate, rate of excretion |
| Influencing viral action | |
| Conditional influence | Hormonal and immunological effects |

**Coclastogen** — a factor that enhances the clastogenicity of a genotoxicant. Examples are bromodeoxyuridine or iododeoxyuridine which increase the rate of chromosome type aberrations caused by the treatment of human lymphocytes in vitro with the clastogen, methyl methanesulfonate (see Kang et al.[498]). Another example presented by Whiting et al. is glutathione, which enhanced the clastogenic effect of selenite and selenate in Chinese hamster ovary cells.[1084]

**Codon** — a sequence of three adjacent nucleotides in m-RNA that code for an amino acid (or chain termination). Any triplet of nucleotides in DNA or RNA (if RNA is the carrier of primary genetic information as in some viruses) that codes for a particular amino acid or signals the beginning or the end of the message.

**Comutagen** — a factor that enhances the mutagenicity of a genotoxicant. One example is norharman which has been reported by Wakabayashi et al. to enhance or newly evoke the mutagenicites of aniline, o-toluidine, yellow OB, 4-dimethylaminoazobenzene, and a variety of N-nitrosoanilines.[1066] Other examples discussed by Rossman are metals which can act as comutagens by inhibiting the repair of damage to DNA caused by a genotoxicant such as arsenite.[857] An example presented by Garro et al. could be applied to the consumption of alcoholic beverages.[306] They reported that chronic ethanol ingestion in rats resulted in an increase in hepatic microsomal dimethylnitrosamine demethylase activity and in an increase in hepatic microsomal activation of dimethylnitrosamine to a mutagen.

**Conflict of interest** — presence of opposing tendencies — one for the common good, the other for personal aggrandizement; an internal battle between the forces of greed and fairness; in an individual or group the opposing actions of incompatibles, one for the public good and the other for personal gain.

**Congenital defect** — an abnormality present at birth; it may be determined genetically or by external influences during intrauterine life. The external influence can be exposure to an environmental genotoxicant. Examples of preliminary data indicating possible occupational hazards for operating room personnel have been given by Spence.[959] They reaffirmed the increased incidence of spontaneous abortion among female physicians working in the operating room and an increase of congenital abnormalities in their offspring. In addition male anesthetists had an increased incidence of hepatic disease and of congenital abnormalities in their offspring.

**Contaminant** — a pollutant which renders the main material unfit for ordinary or scientific use. Some of the materials which can be contaminated are shown in Table 3.