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Cell division is a fundamental property of all living organisms. In multicellular organisms, life starts from a single cell and evolves to adulthood through cell division and differentiation. An elaborate system of controls tightly regulates cell division to the requirements of the organism. Any aberrations in this system may lead to autonomous cell division, which is the hallmark of cancer (Murthy, 2000).

After cell division, the two newly formed daughter cells of a healthy tissue enter one of the following phases, depending on the homeostatic requirements of the tissue:

1. They may die
2. One of them may go into a quiescent state as in the case of stem cells or both may differentiate and mature to replace dying functional cells in the tissue
3. Re-enter the division cycle.

However, in cancer tissue, the cells re-enter the division cycle autonomously to the detriment of the organism. What makes the cells take this militant path? The answer to this question lies in the genes that control cell division cycle.
The cell proliferation system is resistant to mutations. DNA repair and apoptosis provide a powerful defense against carcinogenesis. Oncogenic mutations must not only produce continuous growth signal, but also escape the negative control of tumor suppressor genes. Hence, development of neoplasm requires co-operation among several mutated genes. A classic example of this multi-gene, multi-step process of carcinogenesis is provided by human colorectal cancer. Progression from normal epithelium to hyperplastic epithelium, to dysplastic epithelium, to benign adenomatus polyps, to localized carcinoma, to metastatic carcinoma requires five to six genetic events. Similarly, cancers of breast, colon, rectum, lung, etc., exhibit multiple gene alterations.

Cancer, a global problem, is one of the leading causes of death throughout the world. Annual deaths from cancer exceed 4.5 million. One type of cancer may be more prevalent in a particular region or country than other types, which could be more prevalent in another country. Cancer has a geographical distribution. More than 150 different cancer types have been recognized. Of all cancer types, hematologic malignancies (leukaemia and lymphoma) represent only 10%, whereas 90% of cancers are of solid tumor types (Pathak, 2003).

The most common cancers ranked by annual worldwide incidence, are breast, colo-rectal, lung, stomach, head and neck, prostate, cervical and
skin cancer, of which melanoma is the most lethal. Of all these cancer types, the majority are the results of an interaction between the person's genotype and environmental exposure. Differences in the ethnicity of human populations and differences in their country-specific environments may explain the geographical distribution of this group of dreadful diseases that we call cancer.

As we stand at the beginning of a new millennium, we have to ask the question whether we are winning the war against cancer. It is important to critically review the pattern and pace of progress in Oncology and our preparedness to meet the challenges that lie ahead. For the year 1985, it was estimated that new cancer cases worldwide were 7.6 million (Parkin et al., 1993) and 5 million persons died from the disease (Pisani et al., 1993). Half of these new cancer cases and cancer deaths were in the developing countries. The World Health Organization has estimated that by the year 2015, there will be 15 million new cancer cases annually and approximately two thirds of these will be in the developing countries (Stjernswald et al., 1994). In India, while infectious diseases and malnutrition is undoubtedly a bigger problem, cancer is becoming an increasingly serious public health problem (Dinshaw et al., 2003).

As in most developing countries, the general health and socio-economic indices are not up to the mark in India. The population is
increasing and has already crossed the one billion mark with two thirds of Indians living in villages. Only two thirds of males are literate and for females the situation is even worse with only a third being literate. In cities and towns, safe drinking water is not available in 19% households, 24% houses have no electricity and 36% have no toilet facilities (Gupta and Mittra, 2002). The life expectancy has gradually increased to about 60 years now.

The types of cancer occurring more frequently are different in various parts of the world and depend on the pattern of carcinogen exposure and genetic susceptibility of the population (Tomatis, 1990). In the Indian subcontinent head and neck cancers are the commonest cancers in males and third commonest in females due to a particular pattern of chewing tobacco in betel quid, gutkha, etc., (Sanghvi and Notani, 1989).

Cancer is a group of complex diseases of old age. Some cancers, particularly lung and breast, are more common in older people. This may be due to smoking, poor diet or exposure to environmental carcinogens. Previously, it was suggested that, environment and lifestyle are the major causes of cancer development. About 90% of cancers occur in epithelial tissues and clearly represent the result of interactions between host factors (genetic constitution, health, age and nutritional status) and the environment. Genetic abnormalities by themselves are believed to be
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responsible for only a small fraction of neoplasms. By contrast, an estimated 80 – 90% of cancers are thought to be preventable through the identification and control of environmental factors exerting their clastogenic effects on the genetic and acquired traits that modify individual response (Pathak and Dhaliwal, 1991).

In all reality, genetics loads the gun but environment pulls the trigger. The high incidence of specific cancers in particular professions may indicate a close relationship between occupational agents and the occurrence of cancer. Percival Pott was the first to discover excessive cancers of the scrotum among chimney-sweepers (cf: Pathak, 2003). Benzo(a)pyrene, present in coal tar, is one of the most potent carcinogens and may be responsible for the induction of skin cancer in individuals exposed to coal tar. Air pollution from motor vehicles, hazardous waste products, logging sites, agricultural fertilizers and pesticides (causing water pollution), fire-fighting exposure, laundries, the transportation industry, construction sites, power generators and toxicological research laboratories are well-known primary sources of exposure to occupational and environmental carcinogens (Pathak and Dhaliwal, 1991).

Cancer is the second leading cause of death in the US, exceeded only by heart disease. In the USA, 1 out of every 4 deaths is from cancer-related disease. There is not only a geographical but also an ethnic
distribution of various cancers. Overall, African Americans are more likely to develop cancer than persons of any other racial and ethnic group. During 1990 – 1997, incidence rates were 444.6 per 100,000 among blacks, 402.1 per 100,000 among whites, 272.9 per 100,000 among Hispanics, 279.3 per 100,000 among Asian / Pacific Islanders, and 152.8 per 100,000 among American Indians. Reported rates of female breast cancer are highest among white women (114.0 per 100,000) and lowest among American Indian women (33.4 per 100,000). Among women, African Americans have the highest incidence rates of colon and rectum (45.2 per 100,000) and lung and bronchus cancer (45.8 per 100,000) followed by whites, Asian / Pacific Islanders, Hispanics and American Indians, respectively, for both cancer types. African American men have the highest incidence rates of prostate (225.0 per 100,000), colon and rectum (58.3 per 100,000) and lung and bronchus cancers (111.1 per 100,000). Similar to American Indian females, American Indian males have lower reported rates of cancer incidence than men of other racial and ethnic groups (Anonymous, 2001).

**Chromosomes and Cancer:** There is a plethora of evidence to support the statement that chromosomal abnormalities are prerequisites for neoplastic transformation, cancer progression and metastases (Pathak, 1989a,b, 2001; Pathak and Dhaliwal, 1991; Popescu, 1994; Heim and Mitelman, 1995). These abnormalities include numerical as well as
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structural alterations of different chromosomes in various neoplasms.

The 1995 global estimate for cancer indicates 4.8 million new cases and 3.32 million cancer deaths among males; 4.19 million incident cases and 2.47 million deaths among females. 51.6 percent of incident cancer cases and 55.0 percent of deaths occurred in developing countries. Among males in developing countries, lung, stomach, liver, head and neck and oesophageal cancers accounted for more than two-thirds of both incidence and death; among females, breast and cervix cancers accounted for one third of incident cases and one fourth of mortality. Head and neck cancer accounted for a quarter of 359200 incident cases and a fifth of cancer mortality in males in India; among females, cervical cancer accounted for a quarter of 395700 new cases around 1995. Cancers of the uterine cervix, breast and head and neck accounted for half of the cancer burden in females in India (Sankaranarayanan, 2000).

Incidence and mortality from stomach cancer is declining and breast cancer incidence is on the increase all over the world. A high risk of liver cancer is observed in West and South Africa as well as in Southeast and East Asia. Incidence and mortality from lung cancer is on the rise in many developing regions. The incidence of lung cancer in Mumbai, India, continues to be low and rather steady, while breast cancer incidence has been slowly but steadily rising. Mortality from breast and colo-rectal
cancer has just started declining in certain developed countries due to improvements in detection and treatment. Countries with organized cervical cancer screening programs have recorded marked declines in incidence and mortality from this cancer. Prostate cancer incidences are on the rise in many developed countries due to increased detection by prostate specific antigens (PSA). An improvement in treatment has mainly been responsible for decline in mortality from childhood cancers, cancer of the testis and Hodgkin's disease. The emerging cancer patterns in different regions are important indicators for further development of both preventive and therapeutic health services and underscore the need for continuing surveillance.

**Global Cancer Burden (Around 1995):** Globally, head and neck cancer accounted for 8.7 percent of male and 3.2 percent female cases. The variation in incidence of cancers by sub-site of head and neck in different regions is mostly related to the differential distribution of major risk factors such as tobacco / betel quid chewing, cigarette / bidi-smoking and alcohol drinking. While mouth and tongue cancers are more common in the Indian sub-continent, nasopharyngeal cancer predominates in Hong Kong; pharyngeal and / or laryngeal cancers are more common in other populations.

Oesophageal cancer is associated with a variety of nutritional
deficiencies, thermal injury, smoking, chewing and drinking habits in
developing countries, while alcohol and smoking are major risk factors in
developed countries. There has been a remarkable increase in incidence
of and mortality from oesophageal cancer in eastern and central Europe,
particularly in males. Increases in mortality have been observed in
England and Japan. Incidence rates of this cancer in females in India are
among the high rates observed in the world (Sankaranarayanan, 2000).

Stomach cancer is the second most common cancer among males and
the fourth among females worldwide. The intestinal type has been
associated with excessive salt intake, insufficient vegetable and fruit
consumption and infection with *Helicobacter pylori*. It has been suggested
that the increased availability and consumption of vegetables and fruits;
linked with refrigeration, is possibly responsible for declining stomach
cancer incidence and mortality. The increased occurrence of gastric
cardia cancers has been linked with hyper-acidity, gastro-oesophageal
reflux and Barrett's oesophagus. Better diagnostic techniques, particularly
flexible fibroptic endoscopy, have also been implicated in the increased
diagnosis of cardia malignancies (Sankaranarayanan, 2000).

Colo-rectal cancer is the third most common cancer among males and
second in women worldwide. Colon cancer is associated with diets high in
energy, fats and animal proteins and low in fresh fruits, vegetables and
fibres as well as less physical activity. Rectal cancer has a similar but weaker association with such factors.

Incidence rates of liver cancer are somewhat stable in regions of China from where incidence data are available. A small decline among males is evident in Singapore Chinese, while incidence in females is somewhat stable. However, an increasing trend in mortality is obvious in both sexes. Both, incidence and mortality are rising in males in Japan (Sankaranarayanan, 2000).

Lung cancer is globally the most common cancer in males. The time trends in lung cancer incidence and mortality primarily reflect the patterns of cigarette smoking. It is now one of the leading causes of death in developed countries and rising incidence in several parts of the developing countries. Changes in risk factors other than cigarette smoking can also affect trends in lung cancer incidence and mortality. In men, several populations the U.S., Northern and Western Europe have already experienced the peak incidence of lung cancer and rates have just started to decline. On the contrary, incidence and mortality rates are rapidly increasing in Southern, Central and Western Europe. In females, the populations in the US and UK seem to have already surpassed the peak in incidence, while the rates are still increasing in many European countries. The incidence in males seems to have leveled off in recent
years in Canada, but rates continue to increase among females and the mortality is expected to continue rising. An increase in lung cancer mortality in males is observed in most countries. Incidence and mortality are increasing in both sexes in Japan. The rates seem to be leveling off in Chinese populations in Singapore and Hong Kong, while the incidence rates are still increasing in populations in mainland China. Both incidence and mortality have started declining in most populations in Australia and New Zealand.

Breast cancer is the most common cancer among females worldwide. It is remarkable that breast cancer incidence rates have consistently increased in all populations of the world for which data are available uninterruptedly for a long period of time. In many countries, the incidence is still increasing at all ages. It is speculated that increases in mammographic screening in developed countries and the improvements in data collection in developing countries might account for some increases observed. Incidence rates in the US showed a dramatic increase between 1973 and 1990, after which the rates leveled off (Wingo et al., 1998). This increase is due to the result of screening and seems to be almost entirely due to increases in incidence of localized disease. Survival has improved since 1980 for both pre- and post-menopausal women for both, localized and regional disease, as a result of improvements in treatment which were introduced in the early eighties.
The mortality pattern in Canada is similar to that observed in the US. In South America, incidence and mortality have increased in all populations from which data are available.

In UK, the incidence rate of breast cancer, considerably increased after the introduction of screening in 1988, particularly in the 50 - 64 age group subjected to screening. A recent decline in mortality rates in all age groups has been observed (Peto, 1998). In France, Italy and Spain both incidence and mortality have been rising, though some reduction has been noted in the young age groups in Italy and France. In Sweden, Norway and Switzerland, the mortality has declined. The mortality reductions observed in the US, Canada and northern Europe, seem to be due to the result of improvements in treatment and is too recent to ascribe to screening. However, the reasoning for declines in mortality from breast cancer is a matter of intense debate as of now.

The increases in incidence of breast cancer in Mumbai, India; Shanghai and Hong Kong, China has been less marked than those observed in Singapore and Japan. Mortality has decreased in Hong Kong, but rising in Singapore and Japan. Incidence is on the rise both in Australia and New Zealand, while mortality has leveled off in Australia, but it is rising in New Zealand.
Estimates for 1995 indicate that breast cancer has just overtaken from cervix cancer as the most common cancer among females in developing countries; it is the third most common cancer in females worldwide with 80 percent of the cases occurring in developing countries. Human papilloma virus has been convincingly identified as the most important cause for cervical cancer. The mortality rates have recently shown small declines in Chile and Uruguay. Little change is seen in mortality for other South American populations. In Canada, which has a countrywide mass screening program, incidence and mortality rates have decreased steadily. In the US, a rapid decrease in incidence and mortality rates has been observed in all populations. Overall decline in incidence and mortality has been observed in Europe, these being particularly striking in Finland, Slovenia, Sweden and Switzerland. A decrease in incidence has been observed in most Asian populations. The incidence has markedly declined in Shanghai, China (over 50 percent every five years) as opposed to somewhat lower decline in Mumbai, India and in Singapore. The downward trend in Mumbai has been attributed to the upward shift in age of marriage. The decline in incidence and mortality has been rather small in New Zealand and Australia (Sankaranarayanan, 2000).

The causes of ovarian cancer are poorly understood. However, parity and combined oral contraceptives have been consistently identified as possible protective factors. The protective effect of oral contraceptive use
can be as high as 80 percent depending on the duration of use. The survival from ovarian cancer has also increased in recent years, possibly due to early diagnosis and combination chemotherapy with platinum compounds. In most European populations the incidence and mortality from ovarian cancer is declining. An increase in mortality has been observed in some countries such as Yugoslavia, Spain, Greece and Portugal. Incidence and mortality have increased in Japan and Hong Kong, while these are decreasing in Australia and New Zealand and in most populations in North America.

Prostate cancer is the third most common cancer among males worldwide. Increased detection of prostate cancer by PSA has led to enormous increase in the incidence of prostate cancer in these countries. Following a period of steady increase in earlier years, the recorded incidence increased dramatically in the late eighties. In US, Canada and Australia, the peak in incidence has already been experienced and declines have occurred since 1994. Though prostate cancer is less common in Asian populations, continuing increase in incidence has been observed in Japan, Hong Kong and Singapore. The rates have remained stable in Mumbai, India and Shanghai and China. Mortality is increasing in most countries from where data are available. However, there have been recent declines in mortality in the US (Wingo et al., 1998), Canada (Meyer et al, 1991) and Australia (Threfall, 1998).
The incidence of bladder cancer has been increasing in almost all populations in Europe while mortality has been declining. Incidence has increased in Japan, while rates remained stable in Mumbai, India; Shanghai, China and Singapore; the incidence has declined in Hong Kong. Mortality has fallen sharply in Japan and Hong Kong. Incidence and mortality rates have registered a decline in Australia and New Zealand. Incidence rates are increasing in most populations in the US and Canada. Mortality rates have declined steadily in these two countries.

The incidence of Hodgkin's disease is either stable or declining in most regions in Europe in contrast to the increasing trend in both sexes for Non-Hodgkin's lymphoma. Mortality has declined in almost all countries in Europe. A stable trend in incidence is observed in most Asian populations, Canada and US, while it has declined in Australia and New Zealand. Mortality from Hodgkin's disease has declined in Japan, Hong Kong, Australia and New Zealand, US and Canada. The increase in incidence and mortality in certain countries such as the US has been steady and sharp.

Increases in incidence of leukaemias have been observed in populations in Germany, Spain, UK, Denmark, Hungary and Scotland; in most other European population incidence remains stable. There have been impressive reductions in mortality in both sexes in Netherlands,
Switzerland, Ireland, Scotland and in the Nordic countries (except Denmark) since 1970 and in UK since 1975. The increase in mortality has leveled off in Spain and Portugal, while in some populations in Japan, Hong Kong, Singapore, Australia and New Zealand while it is more or less stable in populations in China and India. While, mortality is rising in Japan, Hong Kong, recent declines have been observed in Australia and New Zealand. There has been a little change in incidence in Central and South America. While, incidence has increased in populations in Canada, it is stable in most populations in the US. Mortality rates are declining in both countries. In countries with declining mortality, the trends are marked in younger than older persons. The decrease in mortality reflects the improvements in treatment and survival, particularly in childhood leukaemia.

Cancer of the pancreas accounts for less than two percent of cancers in most regions of the world. There has been a general increase in incidence of and mortality from cancer of the pancreas in most European and North American populations. The incidence, still relatively low, has substantially increased in most Asian populations, whereas, it is somewhat stable in Central and South American populations.

Bone tumors constitute one percent of all malignancies in most of the world. Mortality from bone tumors has been declining in almost all
populations, but trends in incidence are less consistent. Incidence has been stable or declining in Europe; declining trends are found in Mumbai and Japan, while, increases in Shanghai and Hong Kong and a stable trend in Australia and New Zealand are found.

Soft tissue tumors constitute one percent of malignancies in many regions. There has been a rapid increase in the incidence of cutaneous malignant melanoma in Caucasian populations in the last three decades, though the rate of increase is decelerating particularly for mortality, in recent years. There is very little change in incidence in Indian, Chinese and Japanese populations.

The incidence of testicular cancer, which constitutes less than one percent of cancers in the world, is increasing in Europe, North America, New Zealand and Australia, though the increase is somewhat less rapid in North America and Australia. Mortality has fallen substantially in these populations. The incidence in Asian populations has changed very little, except in Japan, where it has increased rapidly and mortality is declining at 15-20 percent every five years.

The rapid declines in mortality are consistent with remarkable improvement in survival after the widespread introduction of cisplatinum containing treatment combinations after the 1970s.
An increase in incidence of and mortality from cancer of the kidney is observed in all parts of Europe, Japan, Australia, New Zealand and in almost all North American populations. There has been very little change in incidence and mortality in Central and South American countries. Increases in thyroid cancer incidence, particularly in young adults, have been reported from populations in Northern Europe, and US; mortality has been declining in most populations. There has been a slow overall increase in the incidence of brain tumors in many regions of the world, but this has to be interpreted in the background of advances in diagnosis by imaging. A modest increase in mortality is observed in populations in the US and Western Europe.

There has been a marked decline in mortality from childhood cancers in developed countries due to advances in treatment. Improved survival of children receiving treatment according to well-defined protocols has been associated with declines in mortality from acute lymphoblastic leukemia, lymphoma, Wilm's tumor, medulloblastoma, rhabdomyosarcoma and Ewing's tumor.

A detailed examination of trends in cancer incidence and mortality reveals a complex pattern of increases or declines in different regions of the world, some of which are related to changes in the prevalence of specific exposures (e.g., smoking, HIV infection) or advances in detection
(e.g., cervical cytology, mammography, endoscopy, PSA), early detection (e.g., colo-rectum, cervix, breast, melanoma) and treatment (e.g., adjuvant treatments in colo-rectal, breast and testicular cancers; treatment advances in Hodgkin’s lymphoma, acute lymphatic leukemia). The reasons behind certain trends are poorly understood (e.g., decline in stomach cancer). The emerging cancer patterns in these regions are certainly important indicators for further development of both preventive and therapeutic health services and underscore the need for continuing surveillance. The declines in incidence of and mortality from certain cancers in widely varying regions are certainly encouraging. These patterns emphasize the need for further efforts in cancer control to pave the way for reducing the cancer burden and suffering in future.

What causes these genetic events that turn normal genes to militant ones? Normal DNA metabolism itself produces significant amount of DNA damage. The DNA repair enzymes, however, repair most of these damages. The most important external causes of oncogenic events are the use of tobacco and high fat diet. Nearly two-third of all human cancers, which are wholly preventable, are caused by these two factors. About 10% of cancers are inherited. The remaining are due to environmental factors such as ionizing radiations, UV radiations and chemicals including drugs.
getting cancer (Gibbs, 2003).

Biologists estimate that more than 10 million billion cells must cooperate to keep a human being healthy over the course of an 80-year life span (Gibbs, 2003). If any one of those myriad cells could give rise to a tumor, why is it that fewer than half the population will ever contract a cancer serious enough to catch a doctor's attention? One explanation is that a cell must acquire several extraordinary skills to be malignant. "Five or six different regulatory systems must be perturbed in order for a normal cell to grow as a cancer," asserts Robert A. Weinberg of the Whitehead Institute at the Massachusetts Institute of Technology. Cancer cells continue dividing in situations in which normal cells would quietly wait for a special chemical signal — say, from an injured neighbor. Somehow they counterfeit these pro-growth messages. Conversely, tumor cells must ignore "stop dividing" commands that are sent out by the adjacent tissues they squeeze and by their own internal aging mechanisms.

All cancerous cells have serious problems of some sort with their DNA, and as they double again and again, many cells in the resulting colony end up far from the blood vessels that supply oxygen and nutrients. Such stresses trigger autodestruct mechanisms in healthy cells. Tumor cells find some way to avoid this kind of suicide. Then they have to persuade nearby blood vessels to build the infrastructure they need to thrive.
A fifth superpower that almost all cancers acquire is immortality. A culture of normal human cells stops dividing after 50 to 70 generations. That is more than enough doublings to sustain a person through even a century of healthy life. But the great majority of cells in tumors quickly die of their genetic defects, so those that survive must reproduce indefinitely if the tumor is to grow. The survivors do so in part by manipulating their telomeres, gene-free complexes of DNA and protein that protect the ends of each chromosome.

Tumors that develop these five faculties are trouble, but they are probably not deadly. It is the sixth property, the ability to invade nearby tissue and then metastasize to distant parts of the body, that gives cancer its lethal character. Local invasions can usually be removed surgically. But nine of every ten deaths from the disease are the result of metastases.

Only an elite few cells in a tumor seem to acquire this ability to detach from the initial mass, float through the circulation and start a new colony in a different organ from the one that gave birth to them. Unfortunately, by the time they are discovered, many cancers have already metastasized — including, in the U.S., 72 percent of lung cancers, 57 percent of colorectal, and 34 percent of breast. By then the prognosis is frequently grim.
Changes to cancer genes endow the cell with one or more superpowers, allowing it to outbreed its neighbors. The cell passes abnormalities in its DNA sequence on to its descendants, which become a kind of clone army that grows to the limits of its capacity.

Cells normally have two copies of every chromosome — one from the mother, the other from the father — and thus two copies, or alleles, of every gene. A mutation to just one allele is enough to activate an oncogene permanently. But it takes two hits to knock out both alleles of a tumor suppressor gene. Four to ten mutations in the right genes can transform any cell.

According to Jarle Breivik of the University of Oslo, in a “war zone,” where a carcinogen or other stressor is continually inflicting damage to cells, normal cells stop dividing until they have completed repairs to their DNA. Genetically unstable cells get that way because their DNA repair systems are already broken. So they simply ignore the damage, keep on proliferating, and thus pull ahead. But what jumbles the chromosomes in the first place? No genes have yet been conclusively identified as master genes, although several strong suspects have surfaced. German A. Pihan of the University of Massachusetts Medical School and his co-workers may have uncovered a clue in their study, published in March, of 116 premalignant tumors caught before they had invaded neighboring tissues of
the cervix, prostate and breast. 30 to 72% of the growths contained defective centrosomes, structures that appear during cell division to help separate the newly duplicated chromosomes from the originals. Unsurprisingly, most of those cells were aneuploid (Gibbs, 2003).

On the other hand, may be cells can become malignant even before any master genes, oncogenes or tumor suppressor genes are mutated. Peter H. Duesberg and Ruhong Li of the University of California at Berkeley have put forth a third theory: nearly all cancer cells are aneuploid (leukemia being one exception) because they start that way. Lots of things can interfere with a dividing cell so that one of its daughter cells is cheated of its normal complement of 46 chromosomes and the other daughter is endowed with a bonus.

Most aneuploid cells are stillborn or growth-retarded. But, in the rare survivor, Duesberg suggests, the dosage of thousands of genes is altered. That corrupts teams of enzymes that synthesize and maintain DNA. Breaks appear in the double helix, destabilizing the genome further. "The more aneuploid the cell is, the more unstable it is, and the more likely it will produce new combinations of chromosomes that will allow it to grow anywhere," Duesberg explains (Gibbs, 2003).

There are no known means of selectively killing cells with abnormal
chromosomes. But a biopsy that turns up a surfeit of aneuploid cells might warrant careful monitoring or even preventive surgery in certain cases. One day, science will produce a definitive answer to the question of what causes cancer. It will probably be a very complicated answer, and it may force us to shift our hope from drugs that cure the disease to medicines that prevent it. Even without a clear understanding of why, doctors have discovered that a daily baby aspirin seems to prevent colon adenomas in some adults. The effect is small. But it is a step from chemotherapy toward a better alternative: chemoprevention.

TREATMENT OF CANCER

There are several methods of cancer treatment. The important ones are as follows:

SURGERY: "Surgical treatment of cancer", Homburger, (1957) remarks, "is as old as surgery itself". In the Ebers Papyrus (circa 1550 B.C.), there are references to the treatment of "tumors" by surgery. Homburger also points out that the basic principle of modern surgery for cancer is probably not much different from that which guided the surgeons in ancient times, viz., "to remove all of a neoplasm whenever it is possible to do so without too much harm to the patient."

Principle: Surgery for cancer rests on a down-to-lesion approach
that permits one to be satisfied that the cancer has been excised from beyond its gross and microscopic limits. "Surgery," in the words of Smithers (1960), "simply removes the anatomical source of the trouble." This mere removal often provides temporary or permanent, partial or complete, relief from anatomic distortion and physiologic disturbances as may result, say, from an obstruction, pressure phenomenon and the like. The origin of a majority of the cancers from over epithelial surfaces predisposes them to ulceration, fungation and hemorrhage. Surgical removal obviates these complications.

Most cancers are chemo-resistant, many are radio-resistant, but few are knife-resistant as far as mere elimination of an overt focus of cancer is the aim. Most of the organs that are a common site for cancerogenesis lend themselves to resection. "Cancer surgery is different from other types of surgery, because instead of saving as much normal tissue as possible, the cancer surgeon attempts to remove the normal tissue surrounding the tumor..." (Khanolkar, 1958).

The commonest site for neo-occurrence of (second primary) cancer is the same organ that was the seat of the first cancer (Warren and Ehrenreich, 1944). Complete resection of an organ at the time of surgical removal of the first primary cancer obviates the possibility of a neo-occurrence in the same organ. The next common site for neo-occurrence
is the paired member of the first organ affected (breast, ovary, testis, kidney); the paired member may even harbor a silent cancer at the time the first cancer is being treated. The cognizance of the innocent-looking contra-lateral organ as the actual or potential site for second cancer has led to the advocacy of simultaneous removal of both the organs – ovaries (Munnell and Taylor, 1965), adrenals (Smithwich et al, 1971) and breasts. The advocacy of "routine simultaneous prophylactic simple mastectomy", certainly aims at killing two carcinomas with one stroke of knife. Pack (1951) has been very forceful in championing bilateral mastectomy: "The most common pre-cancerous disease of the breast is the one (breast) which remains after mastectomy."

Advantages: In the telling words of Smithers (1960), the outstanding advantage of surgery is that "success when it comes, is immediate and complete." Talking about the "Progress in the Treatment of Breast Cancer," Smithers (1952) observes that surgery removes the anxiety of the presence of a lump in the breast – a statement applicable to cancer at many other sites. Such a built-in advantage with surgical therapy stems from the fact that the surgeon is often in a position to claim that he went, he saw, and he conquered, albeit regionally.

Garb (1968) generalizes that at least 90 per cent of all cancer cures that have been obtained in the past have been a result of surgical
intervention. Common cancers in man such as of thyroid, lung, stomach, colon, brain and breast are best treated by surgery (Pennybacker, 1958; Higgins and Beeke, 1967; Overholt et al., 1970).

Surgery, apart from the gross mutilation that it may inflict locally or the homeostatic disturbances it may cause after resection, say, of endocrine gland/s, is attended by the least number of systemic overtones in direct contrast to those accompanying radiotherapy or chemotherapy. With surgery, the hair does not fall off, the intestinal mucosa does not peel off, and the bone marrow does not get switched off. In other words, surgery does not exact from the patient the pansomatic cellular toll that radio- or chemotherapy does. Surgery, unlike radio- or chemotherapy, is incapable of acting as a cancerogen, or more truly, as a cancer-preponer.

Surgery - the down-to-lesion therapy - has a built-in potential for infinite survival. Therapies may come and therapies may go, but surgery will stay forever. The very nature of the cancerous, acancerous, and procancerous cells of the human body will ensure the continuing hold of surgery in the therapy of cancer.

Disadvantages: Surgery, by its very nature, is regionally, megamutilative, making the neighboring normal tissues pay a heavy price. A “major” amputation (McPeak et al., 1963) for a hardly visible
melanocarcinoma on the foot is an example in point. At times, the strafing of normal tissues is carried too far in procedures labeled as super radical or extended radical, although with far from predictable therapeutic success.

Two inherent disadvantages of surgery are promotion of paraprimalization of cancer by “operative manipulation,” and possible implantation of cancerous cells into juxtaprimal sites or elsewhere (Crile, 1956).

**Limitations:** The apparent supreme efficacy of surgery in dealing with a cancerous lesion at the primal site pales into an incurable impotency against those cells that jumped the fence to set up paraprimal foci elsewhere. Macdonald (1951), discussing radical procedures for carcinoma breast, comments that if a drastic increase in the extent of surgical resection could better the end-results, the same should have been achieved by now; the palpable failure is simply evidence of “the presence of disease beyond the limits of the conventional procedure, either cutaneous or lymph nodal”

**RADIATION:** Radiation therapy, like chemotherapy but unlike surgery, should be looked upon as *in situ* attack on cancer cells, killing the cells that are resting or multiplying in their primal or Para primal home. The
needlessness of ablation, inevitable with surgery, renders radiotherapy a useful weapon at sites that cannot be resected without killing the patient.

**Principle:** Not long after the discovery of roentgen rays and radium in the last decade of the nineteenth century, medical men started using the truly double-edged weapon of radiation in cancerology - employing the cancricidal edge in the treatment of cancer and the cancerogenic edge in the induction of cancer in animals. It appeared that the cancerogenic edge did not assert itself when the cancricidal edge was being used and it became convenient to assume that the mysterious and powerful radiational beam selectively hunted out the cancerous outlaws, leaving the normal cells unmolested.

The divisibility of cancer cells does not always render them vulnerable to the radiational attack. Many a cancer melts before the therapeutic beam, only to emerge as a radio-resistant mass that grows in the very teeth of radiotherapy. The obstinate invulnerability of dividing cancer cells and the unfortunate vulnerability of the normal dividing (or divisible) cells of the body makes impossible for any therapist or therapy to claim: I shall kill *the cancer, the whole cancer, and nothing but the cancer,* so help me GOD;

**Nature of (Ionizing) Radiation:** The various forms of radiation are
electromagnetic waves and/or discontinuous quanta of energy acting as corpuscular matter, giving rise, directly or indirectly, to a common phenomenon, ionization, on their interacting with matter (Homburger, 1957; Anonymous, 1962; Berdjis, 1971a,b). X rays are ionizing particles at average distances of 0.1 millimicron, while, alpha rays are ionizing particles at average distances of 0.0002 millimicron; amongst electromagnetic waves, the X rays, radium rays and cosmic rays occupy the extreme of the shortest wave lengths known: gamma radiation as compared to X radiation is shorter in wave length and possessed of greater energy.

The various forms of therapeutic radiation are: Conventional X rays (50-500 kv); megavolt X rays (1000-2000 kv); radium rays (gamma rays of nearly 2^6 volt energy); betatron, synchroton, or linear accelerator beams which generate either electron beams or megavolt X rays; radioactive isotopes such as ^{32}P providing beta particles, ^{131}I giving off beta and gamma rays, and ^{60}Co, ^{198}Au, ^{82}Br, ^{192}Ir and ^{182}Ta all providing gamma rays; high-LET radiations such as accelerated protons, fast neutrons, negative pi-mesons or pions, and the short range alpha particles and lithium particles from neutron capture by boron-10. For “neutron capture therapy” (Bond et al., 1967), ^{10}B has been employed (Homburger, 1957; Sweet et al., 1963; Bond et al., 1967). Although ^{10}B (boron-10) is the capture element most commonly employed, ^{6}Li, higher-Z fissionable
nuclei, or other isotopes with a high cross-section for capture of thermal neutrons can theoretically be used (Bond et al., 1967). “If the capture element can be incorporated into compounds that effectively localize selectively in tumor versus normal tissue, and if both normal and tumor tissues are exposed to thermal neutrons, the dose of radiation delivered to the tumor will exceed that of normal tissue, leading to a situation that in principle is favorable for radiotherapy.” (Bond et al., 1967).

The Healing Edge of Radiotherapy: The progress made in radiotherapy of cancer in the past decades has established it as an indispensable medical weapon in the fight against this disease. Cures are possible with radiotherapy and depend on the ability of the radiational beam to achieve a timely total kill of the cancer (stem) cells accompanied by an absence — temporary or permanent — of recruitment of normal cells into the cancerous army. Such a cure also necessitates the absence of a distant cancerous government/s set up by the fleeing cells from the primal site. Some individuals having a cancer curable by irradiation manage to fulfill the foregoing difficult conditions so as to obtain a cure that is essentially patient-dependent.

The Hurting Edge of Radiotherapy: Radiotherapy, like chemotherapy, just kills cells, normal or cancerous. Radiotherapy like all other therapies, does nothing to the intrinsic cancerism or the acancerous diathesis of a
patient so that the ability of body cells to turn cancerous eventually outwits the radiational attack, and kills the patient. Radiotherapy accelerates neo-canceration: while it is busy killing cancer cells with its right hand, it is actively dragging with its left hand the normal procancerous cell to an earlier-than-scheduled cancerous change. It is always a double-edged weapon and the apparent benignity of its harmful edge is entirely a function of the patient's cellular program and senescent trajectory.

Another feature that underlies the built-in failure of radiotherapy (or chemotherapy) is that unbelievable and unpalatable lesson driven home by studies on cellular kinetics that normal cells multiply faster than cancerous cells. With the inherent large backdrop in a patient with cancer of normal dividing cells dividing at cancerous rates in such areas as the bone marrow and the gut, normal cell kill becomes a certainty, cancer cell kill a probability. "The cells of bone-marrow and those lining the gastrointestinal tract are both essential to life. Accordingly, it seems that medications and procedures aimed at killing young, rapidly multiplying cells will probably not kill all cancer cells before they kill the patient."

In explaining the failure of radio- or chemotherapy, recourse is taken to the concept of first order kinetics or what one may call quantum kill which implies that "a given dose of an antineoplastic agent kills a constant percentage of malignant cells irrespective of their total number and that
the survivors continue to divide at the previous rate.

**CHEMOTHERAPY**: Among all the subspecialties of internal medicine, medical oncology may have had the greatest impact in changing the practice of medicine in the past two decades, as curative treatments have been identified for a number of previously fatal malignancies such as testicular cancer, lymphomas and leukemia. New drugs have entered clinical use for disease presentations previously, either untreatable or amenable to only local means of therapy, such as surgery and irradiation. The nature of and basic approaches to cancer treatment are constantly changing. Clinical protocols are now exploring genetic therapies, manipulations of the immune system, stimulation of normal hematopoietic elements, and induction of differentiation in tumor tissues and inhibition of angiogenesis. Research in each of these new areas has led to experimental or, in some cases, routine applications for nonmalignant disease. The same drugs used for cytotoxic antitumor therapy have become important components of immunosuppressive regimens for rheumatoid arthritis (Methotrexate and Cyclophosphamide), anti-infective chemotherapy (Trimetrexate and Leucovorin) and psoriasis (Methotrexate). Thus, a broad spectrum of medical, surgical and pediatric specialists employ these drugs for both neoplastic and non-neoplastic disease.
Traditionally, cancer drugs were discovered through large-scale screening of synthetic chemicals and natural products against animal tumor systems, primarily murine leukemias. The agents discovered in the first two decades of cancer chemotherapy (1950 to 1970) largely interacted with DNA or its precursors, inhibiting the synthesis of new genetic material or causing irreparable damage to DNA itself. In recent years, the discovery of new agents has extended from the more conventional natural products such as Paclitaxel (TAXOL) and semi synthetics such as Etoposide, both of which target the proliferative process, to entirely new fields of investigation that represent the harvest of new knowledge about cancer biology.

In routine practice, the drugs used fall into two main groups, hormonal and cytotoxic. Hormonal agents are generally much better tolerated than cytotoxic drugs (Rees et al., 1993).

**Hormonal drugs:** These comprise hormones and anti-hormones. Their mode of action is imperfectly understood although their efficacy largely depends on the malignant cells having hormone receptors. Hormonal drugs do not have curative potential by themselves, although it is possible that they may be able to slightly increase the rate of some tumors when used in addition to local treatment.
Cytotoxic drugs: Cytotoxic drugs preferentially affect dividing cells in tumors and their hosts. Their side effects are most apparent in those tissues or organs where there is a rapid cell turnover. These include the bone marrow, gastro-intestinal epithelium and hair follicles.

A cytotoxic drug usually exerts its effects by one or more of the following:

1. Interfering with the production of DNA (e.g. anti-metabolites such as Methotrexate and 5-Fluorouracil)

2. Damaging DNA [e.g. alkylating agents such as Cyclophosphamide and Melphalan, antibiotics such as Adriamycin and Actinomycin D, nitrosoureas such as 1,3-bis-(2-chloroethyl)-1-nitrosourea (BCNU) and 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU)].

3. Damaging the mitotic spindle (e.g. Vinca alkaloids such as Vincristine and Vinblastine).

Some drugs are effective throughout the cell cycle (e.g., the alkylating agents and Adriamycin), while others exert their effect at a particular phase of the cycle (e.g. Methotrexate is effective during DNA synthesis and Vincristine during mitosis).

Malignancies for which cytotoxic chemotherapy can be curative or contribute to cure:
• Choriocarcinoma
• Ewing's sarcoma
• Germ-cell tumors of testis and ovary (teratoma, seminoma, dysgerminoma)
• Hodgkin's disease
• Acute leukemia
• Non-Hodgkin's lymphoma
• Embryonal rhabdomyosarcoma
• Wilms' tumor

Common or significant side effects that may occur with cytotoxic drugs:

• Bone-marrow suppression
• Nausea and vomiting
• Alopecia
• Hair texture and color change
• Skin and nail changes
• Malaise
• Lethargy
• Psychological intolerance
• Taste alteration
• Appetite impairment
• Stomatitis
• Thrombophlebitis at injection site
• Muscle aching
Introduction

- Immunosuppression
- Amenorrhoea
- Carcinogenicity
- Teratogenicity

The most important pharmacological actions of the alkylating agents are those that disturb the fundamental mechanisms concerned with cell proliferation, in particular DNA synthesis and cell division. The capacity of these drugs to interfere with DNA integrity and function in rapidly proliferating tissues provides the basis for their therapeutic applications and for many of their toxic properties. Whereas certain alkylating agents may have damaging effects on tissues with normally low mitotic indices — for example, liver, kidney and mature lymphocytes — they are most cytotoxic to rapidly proliferating tissues in which a large proportions of the cells are in division. These compounds may readily alkylate non-dividing cells, but cytotoxicity is markedly enhanced if DNA is damaged in cells programmed to divide. Thus, DNA alkylation itself may not be lethal event if DNA repair enzymes can correct the lesions in DNA prior to the next cellular division (Hardman and Limbird, 1996).

The diversity of agents useful in the treatment of neoplastic disease is summarized as below (Table 1) of which, alkylating agents are one of the popular drugs used against cancer:
<table>
<thead>
<tr>
<th>CLASS</th>
<th>TYPE OF AGENT</th>
<th>NON-PROPRIETARY NAMES (OTHER NAMES)</th>
<th>DISEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alkylating</td>
<td></td>
<td>Hodgkin's disease, non-Hodgkin's lymphomas.</td>
</tr>
<tr>
<td>Nitrogen</td>
<td>Alkylating</td>
<td>Mechloretamine</td>
<td>Hodgkin's disease, non-Hodgkin's lymphomas.</td>
</tr>
<tr>
<td>Nitrogen</td>
<td>Alkylating</td>
<td>Cyclophosphamide</td>
<td>Acute and chronic lymphocytic leukemias; Hodgkin's lymphomas; multiple myelomas; neuroblastoma; breast, ovary, lung cancer; Wilm's tumor, cervix, testis cancer; soft tissue sarcoma.</td>
</tr>
<tr>
<td>Nitrogen</td>
<td>Alkylating</td>
<td>Ifosfamide</td>
<td>Hodgkin's lymphomas; multiple myelomas; neuroblastoma; breast, ovary, lung cancer; Wilm's tumor, cervix, testis cancer; soft tissue sarcoma.</td>
</tr>
<tr>
<td>Nitrogen</td>
<td>Alkylating</td>
<td>Melphalan (L-sarcolysin)</td>
<td>Multiple myeloma; breast, ovarian cancer</td>
</tr>
<tr>
<td>Ethylenimines</td>
<td>Ethylenimines</td>
<td>Hexamethylmelamine</td>
<td>Ovarian cancer</td>
</tr>
<tr>
<td>and Methylmelamines</td>
<td>Ethylenimines</td>
<td>Thiotepa</td>
<td>Bladder, breast, ovarian cancer</td>
</tr>
<tr>
<td>Alkyl Sulfonates</td>
<td>Alkyl Sulfonates</td>
<td>Busulfan</td>
<td>Chronic granulocytic leukemia</td>
</tr>
<tr>
<td>Nitrosoureas</td>
<td>Nitrosoureas</td>
<td>Carmustine (BCNU)</td>
<td>Hodgkin's disease, non-Hodgkin's lymphomas, primary brain tumors, multiple myeloma, malignant melanoma</td>
</tr>
<tr>
<td>Triazenes</td>
<td>Triazenes</td>
<td>Dacarbazine (DTIC; dimethyltriazenoimid – azolecarboxamide)</td>
<td>Malignant melanoma, Hodgkin's disease, soft-tissue sarcomas</td>
</tr>
<tr>
<td></td>
<td>Triazenes</td>
<td>Temozolomide</td>
<td>Glioma, malignant melanoma</td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>Folic Acid Analogs</td>
<td>Methotrexate (amethopterin)</td>
<td>Acute lymphocytic leukemia; chorio-carcinoma; mycosis fungoides; breast, head and neck, lung cancer; osteogenic sarcoma</td>
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<tr>
<td></td>
<td>Pyrimidine Analogs</td>
<td>Fluorouracil (5-fluorouracil; 5-FU) Floxuridine (fluorodeoxyuridine; FudR)</td>
<td>Breast, colon, stomach, pancreas, ovarian, head and neck, urinary bladder cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cytarabine (cytosine arabinoside)</td>
<td>Acute granulocytic and acute lymphocytic leukemia</td>
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<td></td>
<td></td>
<td>Gemcitabine</td>
<td>Pancreatic cancer, ovarian cancer.</td>
</tr>
<tr>
<td></td>
<td>Purine Analogs and Related inhibitors</td>
<td>Mercaptopurine (6-mercaptopurine, 6-MP)</td>
<td>Acute lymphocytic, acute granulocytic and chronic granulocytic leukemias</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thioguanine (6-Thioguanine; TG)</td>
<td>Acute granulocytic, acute lymphocytic and chronic granulocytic leukemias</td>
</tr>
<tr>
<td></td>
<td>Purine Analogs and Related inhibitors</td>
<td>Pentostatin (2'-deoxycoformycin)</td>
<td>Hairy cell leukemia, mycosis fungoides, chronic lymphocytic leukemia, small cell lymphoma</td>
</tr>
<tr>
<td>Natural Products</td>
<td>Vinca Alkaloids</td>
<td>Vinblastine (VLB)</td>
<td>Hodgkin's disease, non-Hodgkin's lymphomas, breast, testis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vincristine</td>
<td>Acute lymphocytic leukemia, neuroblastoma, Wilms' tumor, rhabdomyosarcoma, Hodgkin's disease, non-Hodgkin's lymphomas, small-cell lung sarcoma</td>
</tr>
</tbody>
</table>

*Contd...*
<table>
<thead>
<tr>
<th>Natural Products (contd.)</th>
<th>Epipodophyllotoxins</th>
<th>Antibiotics</th>
<th>Enzymes</th>
<th>Biological Response Modifiers</th>
<th>Miscellaneous Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etoposide Teniposide</td>
<td></td>
<td>Dactinomycin (Actinomycin D)</td>
<td>Dactinomycin (Actinomycin D)</td>
<td>Dactinomycin (Actinomycin D)</td>
<td>Dactinomycin (Actinomycin D)</td>
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<td></td>
<td></td>
<td>Daunorubicin (Daunomycin; Rubidomycin)</td>
<td>Daunorubicin (Daunomycin; Rubidomycin)</td>
<td>Daunorubicin (Daunomycin; Rubidomycin)</td>
<td>Daunorubicin (Daunomycin; Rubidomycin)</td>
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<td></td>
<td></td>
<td>Doxorubicin</td>
<td>Doxorubicin</td>
<td>Doxorubicin</td>
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<td></td>
<td></td>
<td>Bleomycin</td>
<td>Bleomycin</td>
<td>Bleomycin</td>
<td>Bleomycin</td>
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<tr>
<td></td>
<td></td>
<td>Plicamycin (mithramycin)</td>
<td>Plicamycin (mithramycin)</td>
<td>Plicamycin (mithramycin)</td>
<td>Plicamycin (mithramycin)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mitomycin (Mitomycin C)</td>
<td>Mitomycin (Mitomycin C)</td>
<td>Mitomycin (Mitomycin C)</td>
<td>Mitomycin (Mitomycin C)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L-Asparaginase</td>
<td>L-Asparaginase</td>
<td>L-Asparaginase</td>
<td>L-Asparaginase</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Interferon-alfa</td>
<td>Interferon-alfa</td>
<td>Interferon-alfa</td>
<td>Interferon-alfa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cisplatin (cis-DDP)</td>
<td>Cisplatin (cis-DDP)</td>
<td>Cisplatin (cis-DDP)</td>
<td>Cisplatin (cis-DDP)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carboplatin</td>
<td>Carboplatin</td>
<td>Carboplatin</td>
<td>Carboplatin</td>
</tr>
</tbody>
</table>

**Cisplatin (cis-DDP)**: Testis, small-cell lung and other lung, breast, Hodgkin's disease, non-Hodgkin's lymphomas, acute granulocytic leukemia, Kaposi's sarcoma

**Doxorubicin**: Soft-tissue, osteogenic and other sarcomas; Hodgkin's disease, non-Hodgkin's lymphomas, acute leukemias, breast, genitourinary, thyroid, lung, stomach, neuroblastoma

**Bleomycin**: Testis, head and neck, skin, esophagus, lung and genitourinary tract; Hodgkin's disease, non-Hodgkin's lymphomas

**Plicamycin (mithramycin)**: Testis, malignant hypercalcemia

**Mitomycin (Mitomycin C)**: Stomach, cervix, colon, breast, pancreas, bladder, head and neck

**L-Asparaginase**: Acute lymphocytic leukemia

**Interferon-alfa**: Hairy cell leukemia, Kaposi's sarcoma, melanoma, carcinoid, renal cell, ovary, bladder, non-Hodgkin's lymphomas, mycosis fungoides, multiple myeloma, chronic granulocytic leukemia

**Cisplatin (cis-DDP)**: Testis, ovary, bladder, head and neck, lung, thyroid, cervix, endometrium, neuro-blastoma, osteogenic sarcoma
<table>
<thead>
<tr>
<th>Miscellaneous Agents (contd.)</th>
<th>Anthracenedione</th>
<th>Mitoxantrone</th>
<th>Acute granulocytic leukemia, breast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substituted Urea</td>
<td>Hydroxyurea</td>
<td>Chronic granulocytic leukemia, polycythemia vera, essential thrombocytosis, malignant melanoma</td>
<td></td>
</tr>
<tr>
<td>Methylhydrazine Derivative</td>
<td>Procarbazine (N-methylhydrazine)</td>
<td>Hodgkin's disease</td>
<td></td>
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<tr>
<td>Adrenocortical Suppressant</td>
<td>Mitotane (o,p'-DDD)</td>
<td>Adrenal cortex</td>
<td></td>
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<tr>
<td>Aminoglutethimide</td>
<td></td>
<td>Breast</td>
<td></td>
</tr>
<tr>
<td>Adrenocortico-steroids</td>
<td>Prednisone (several other equivalent preparations available)</td>
<td>Acute and chronic lymphocytic leukemias, non-Hodgkin's lymphomas, Hodgkin's disease, breast</td>
<td></td>
</tr>
<tr>
<td>Progestins</td>
<td>Hydroxyprogesterone caproate</td>
<td>Endometrium, breast</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Medroxyprogesterone acetate</td>
<td></td>
<td></td>
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<td></td>
<td>Megestrol acetate</td>
<td></td>
<td></td>
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<tr>
<td>Estrogens</td>
<td>Diethylstilbestol</td>
<td>Breast, Prostate</td>
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<tr>
<td></td>
<td>Ethinyl estradiol</td>
<td></td>
<td></td>
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<tr>
<td>Antiestrogen</td>
<td>Tamoxifen</td>
<td>Breast</td>
<td></td>
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<tr>
<td>Androgens</td>
<td>Testosterone propionate</td>
<td>Breast</td>
<td></td>
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<tr>
<td></td>
<td>Fluoxymesterone</td>
<td></td>
<td></td>
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<tr>
<td>Antiandrogen</td>
<td>Flutamide</td>
<td>Prostate</td>
<td></td>
</tr>
<tr>
<td>Gonadotropin-Releasing Hormone Analog</td>
<td>Leuprolide</td>
<td>Prostate</td>
<td></td>
</tr>
</tbody>
</table>

[Source: Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th Edition. Hardman and Limbird (Eds.) 1996]
ALKYLATING AGENTS

History: Although synthesized for the first time, in 1854, the vesicant properties of sulfur mustard were not described until 1887. During World War I, medical attention was first focused on the vesicant action of sulfur mustard on the skin, eyes and respiratory tract. It was appreciated later, however, that serious systemic toxicity also follows exposure. In 1919, Krumbhaar and Krumbhaar (cf: Chabner et al., 1996) made the pertinent observation that the poisoning caused by sulfur mustard is characterized by leukopenia and in cases that came to autopsy, by aplasia of the bone-marrow, dissolution of lymphoid tissue and ulceration of the gastrointestinal tract.

In the interval between World Wars I and II, extensive studies of the biological and chemical actions of the nitrogen mustards were conducted. The marked cytotoxic action on lymphoid tissue prompted Gilman, Goodman and Dougherty to study the effect of nitrogen mustards on transplanted lymphosarcoma in mice and in 1942 clinical studies were initiated. This launched the era of modern cancer chemotherapy (Gilman, 1963).

In their early phases, all these investigations were conducted under secrecy restrictions imposed by the use of classified chemical-warfare agents. At the termination of World War II, however, the nitrogen
mustards were declassified; a general review was presented by Gilman and Philips (1946). A more recent review is provided by Ludlum and Tong (1985).

Thousands of variants of the basic chemical structure of the nitrogen mustards have been prepared, but only a few of these agents have proven more useful than the original compound in specific clinical circumstances. At present five major types of alkylating agents are used in the chemotherapy of neoplastic diseases: (1) the nitrogen mustards, (2) the ethylenimines, (3) the alkyl sulfonates, (4) the nitrosoureas and (5) the triazenes.

Chemistry: The chemotherapeutic alkylating agents have in common, the property of becoming strong electrophiles through the formation of carbonium ion intermediates or of transition complexes with the target molecules. These reactions result in the formation of covalent linkages by alkylation of various nucleophilic moieties such as phosphate, amino, sulfhydryl, hydroxyl, carboxyl and imidazole groups.

PHARMACOLOGICAL ACTIONS

Cytotoxic Actions: The most important pharmacological actions of the alkylating agents are those that disturb the fundamental mechanisms concerned with cell proliferation, in particular DNA synthesis and cell
division. The capacity of these drugs to interfere with DNA integrity and function in rapidly proliferating tissues provides the basis for their therapeutic applications and for many of their toxic properties. Whereas, certain alkylating agents may have damaging effects on tissues with normally low mitotic indices — for example, liver, kidney and mature lymphocytes — they are most cytotoxic to rapidly proliferating tissues in which a large proportion of the cells are in division. These compounds may readily alkylate non-dividing cells, but cytotoxicity is markedly enhanced if DNA is damaged in cells programmed to divide. Thus, DNA alkylation itself may not be a lethal event if DNA repair enzymes can correct the lesions in DNA prior to the next cellular division. The actual mechanism(s) of cell death related to DNA alkylation are not well understood. There is evidence that, in normal cells of the bone marrow and intestinal epithelium, DNA damage activates a checkpoint dependent on the presence of a normal p53 gene.

The remarkable DNA repair systems found in most cells likely play an important, but as yet poorly defined, role in the relative resistance of nonproliferating tissues, the selectivity of action against particular cell types and acquired resistance to alkylating agents. Detailed information is lacking on mechanisms of cellular uptake of alkylating agents.

**Mechanisms of Resistance to Alkylating Agents:** Acquired resistance
to alkylation agents is a common event, and the acquisition of resistance to one alkylation agent often, but not always imparts cross-resistance to others. While definitive information on the biochemical mechanisms of clinical resistance is lacking, specific biochemical changes have been implicated in the development of such resistance by tumor cells. Among these changes in cells resistant to alkylation agents are: (1) decreased permeation of actively transported drugs, (2) increased production of nucleophilic substances, such as Glutathione, that can compete with the target DNA for alkylation; (3) increased activity of the DNA repair enzymes such as the guanine O\(^\prime\) - alkyl transferase that repairs nitrosourea alkylation; and (4) increased rates of metabolism of the activated forms of Cyclophosphamide to its inactive keto and carboxy metabolites by aldehyde dehydrogenase (Hardman and Limbird, 2001).

**Toxicities of Alkylation Agents:** The alkylation agents differ in their patterns of antitumor activity and in the sites and severity of their side effects. They have in common, a propensity to cause dose-limiting toxicity to bone-marrow elements and to a lesser extent, intestinal mucosa. Most alkylation agents, including nitrogen mustard, Melphalan, Chlorambucil, Cyclophosphamide and Ifosfamide, produce an acute myelosuppression, with a nadir of the peripheral blood granulocyte count at 6 to 10 days and recovery in 14 to 21 days. Cyclophosphamide has lesser effects on peripheral blood platelet counts than do the other agents. Busulfan
suppresses all blood elements, particularly stem cells and may produce a prolonged and cumulative myelosuppression lasting months. For this reason, it is used as a preparative regimen in allogenic bone-marrow transplantation. 1,3-bis-(2-chloroethyl)-1-nitrosourea [Carmustine (BCNU)] and other chloroethylnitrosoureas cause delayed and prolonged myelosuppression involving both platelets and granulocytes, reaching a nadir 4 to 6 weeks after drug administration and reversing slowly thereafter.

In addition to effects on the hematopoietic system, alkylating agents are highly toxic to dividing mucosal cells, leading to oral mucosal ulceration and intestinal denudation. The mucosal effects are particularly significant in high-dose chemotherapy protocols associated with bone-marrow reconstitution, as they predispose to bacterial sepsis arising from the gastrointestinal tract. In these protocols, Melphalan and Thiotepa have the advantage of causing less mucosal damage than the other agents. In high-dose protocols, a number of toxicities not seen at conventional doses become dose limiting.

While mucosal and bone marrow toxicities occur predictable with conventional doses of these drugs, other organ toxicities, although less common, can be irreversible and at times lethal. All alkylating agents have caused instances of pulmonary fibrosis and veno-occlusive disease.
of the liver; the nitrosoureas, after multiple cycles of therapy, may lead to renal failure. Cyclophosphamide and Ifosfamide release a nephrotoxic and urotoxic metabolite, acrolein, which causes a severe hemorrhagic cystitis, a side effect.

Central nervous system toxicity is manifest in the form of nausea and vomiting, particularly after intravenous administration of nitrogen mustard or BCNU. Ifosfamide is the most neurotoxic of this class of agents, producing altered mental status, coma, generalized seizures and paralysis. As a class of drugs, the alkylating agents are highly leukemogenic. Acute non-lymphocytic leukemia, often associated with partial or total deletions of chromosomes 5 or 7, peaks in incidence about four years after therapy and may affect up to 5% of patients treated on regimens containing alkylating drugs (Levine and Bloomfield, 1992). Melphalan, the nitrosoureas and the methylating agent Procarbazine have the greatest propensity to cause leukemia, while Cyclophosphamide is less potent in this regard.

Finally, all alkylating agents have toxic effects on the male and female reproductive systems, causing an often permanent amenorrhea, particularly in perimenopausal women and an irreversible azoospernia in men [(McInnes and Schilsky, 1995) cf: Hardman and Limbird, 1996].
**Background:** Molecular oxygen, now so abundant in our atmosphere is the product of photosynthesis. The appearance of the first blue-green algae, approximately \(2 \times 10^8\) years ago (Echelin, 1970) and the subsequent oxygenation of the biosphere imposed a stringent evolutionary pressure on the many organisms that up to then, had lived and evolved in an anaerobic world. While evolving mechanisms for the utilization of oxygen, they had to develop defenses against it's toxicity. Considering the situation of a common evolutionary pressure applied to a varied biota, it is not surprising that multiple defenses arose and have persisted.

The turnover of oxygen by cells of aerobic organisms is associated with the generation of ROS, including singlet oxygen, \(H_2O_2\), superoxide and hydroxyl radicals (Gille and Sigler, 1995). The dark side of oxygen biochemistry (Valentine et al., 1998; Mates and Sánchez-Jiménez, 1999) refers to the potentially hazardous effects of ROS, such as extensive oxidative damage to membrane lipids (Gutteridge, 1995), DNA (Beckman and Ames, 1997) and proteins (Berlett and Stadtman, 1997) and peroxidation of lipoproteins (Esterbauer and Ramos, 1995).

To cope with oxidative insult, the cell has developed a number of defense strategies, both at the level of oxidative damage repair and reactive oxygen species (ROS) scavenging mechanisms (Mates et al., 1999; Sies, 1993; Cardozo-Páez et al., 2000). Antioxidant
mechanisms comprise redox-active cellular low-molecular-mass compounds such as Glutathione (GSH) or the radical-scavenging vitamins E & C, as well as the enzymatic ROS-metabolizing systems, including Superoxide dismutase, Catalase and GSH peroxidase (Chaudiere and Ferrari-Iliou, 1999; Halliwell, 1999; Hayes and McLellan, 1999).

The aerobic life-style offers great advantages, but is fraught with danger. Complete reduction of a molecule of oxygen to water requires four electrons, and in a sequential univalent process several intermediates will be encountered. These are the superoxide anion radical, hydrogen peroxide and the hydroxyl radical and they are too reactive [Czapski, 1971 (cf: Fridovich,1978)] to be well tolerated within living systems. Nevertheless, the univalent pathway of oxygen reduction does occur and these dangerously reactive intermediates must somewhat be accommodated. The primary defense is provided by enzymes that catalytically scavenge the intermediates of oxygen reduction. The superoxide radical is eliminated by superoxide dismutases, which catalyze it’s conversion to hydrogen peroxide plus oxygen (Fridovich, 1975) and hydrogen peroxide is removed by catalases (Rapoport and Müller, 1974) which convert it to water plus oxygen and by peroxidases (Saunders et al., 1964) which reduce it to water, using a variety of reductants available to the cell.
Introduction

Fig. 1. Scheme of free radical defense mechanisms. Small molecules and enzyme systems have evolved to maintain low steady state concentrations of intracellular free radicals. Free radicals can undergo three major reactions in a cell. Reactions with lipid, protein or DNA may lead to cytotoxicity. Free radicals may be quenched by reactions with small molecules located in cytoplasm or membranes. Finally, a series of enzymes have evolved that scavenge superoxide, hydrogen peroxide and lipid peroxides.

[Source: Freeman and Crapo. 1982. Lab. Invest. 47; 5, 412-426]

Fig. 2. Balance of ROS generation and antioxidative systems. An imbalance of both systems due to either excessive production of ROS (left) or reduced antioxidant defense (right) leads to oxidative stress.

Because antioxidant defenses are not completely efficient, increased free-radical formation in the body is likely to increase damage. The term "oxidative stress" is often used to refer to this effect (Sies, 1991). If mild oxidative stress occurs, tissues often respond by making extra antioxidant defenses. However, severe oxidative stress can cause cell injury and death. Free-radical-induced cell death can proceed as necrosis or apoptosis, and "anti-apoptosis genes" in certain cells appear to encode free-radical scavengers (Sarafian and Bredesen, 1994).

One way of imposing oxidative stress is by the action of certain toxins, namely those that produce free radicals or deplete antioxidant defenses (Halliwell and Gutteridge, 1989; Aust et al., 1993). One particular area of interest is the possibility that the side-effects of several drugs involve increased oxidative damage (Aust et al., 1993; Keizer et al., 1990).

Examples fall into four main groups. First, the toxin is itself a free radical — e.g., nitrogen dioxide (NO₂⁻), the brown toxic gas in polluted air. This compound is a good initiator of lipid peroxidation.

\[
\text{Lipid-H + NO}_2^- \rightarrow \text{lipid}^- + \text{HNO}_2
\]

Second, the toxin is metabolized to a free radical — e.g., carbon tetrachloride is converted to a free radical by hepatic cytochrome P-450.

\[
\text{CCl}_4 \rightarrow \text{Cl}^- + \text{CCl}_3^-
\]

This radical reacts with oxygen to give a peroxyl radical:
\[ \text{CCl}_3^+ + \text{O}_2 \rightarrow \text{CCl}_3\text{O}_2^+ \]

Which is a good initiator of lipid peroxidation (Aust et al., 1993).

Third, the toxin is metabolized to generate oxygen free radicals. Thus, although Doxorubicin’s anti-cancer effect probably interferes with DNA unwinding during replication, it’s major side effects (especially cardiotoxicity) may involve excess of superoxide and hydroxyl radical production (Keizer et al., 1990).

Fourth, the toxin depletes antioxidant defenses. Paracetamol’s metabolism by liver cytochrome P-450 generates a product that reacts with and removes Glutathione. Loss of Glutathione causes secondary oxidation damages, which contributes to hepatic failure in Paracetamol overdose.

Halliwell and Gutteridge (1984), emphasized that oxidative damage could be just as much a consequence of tissue injury as a cause of it. What is exciting at the moment is that in neurodegenerative disease, chronic inflammatory disease, cardiovascular disease, and cancer (the major scourges of life in “advanced” countries), evidence is accumulating to show that free-radical damage is important. Hopefully, this realization will contribute to the development of new preventive and therapeutic strategies. The criteria that are needed to implicate free radicals as
important contributors in the cause of disease have been reviewed (Halliwell et al., 1992).

Hydrogen peroxide is a normal cellular metabolite (Singer and Edmondson, 1974; Chance et al., 1979) as well as a reactive form of oxygen produced during oxidative damage to tissues (Chance et al., 1979). It is formed in all subcellular compartments under appropriate conditions [Boveris et al., 1972 (cf: Jones et al., 1981)] and is also produced in vitro during autoxidation of normal physiological reductants such as reduced GSH [Misra, 1974 (cf: Jones et al., 1981)] and ascorbate [Chance, 1950 (cf: Jones et al., 1981)].

The various processes leading to intracellular H$_2$O$_2$ generation have been discussed frequently with regard to the role of this agent in oxidative cell injury and therefore the conditions for generation and metabolism of H$_2$O$_2$ in intact tissues are of great general interest.

Free radicals are typically molecules that contain one or more unpaired electrons. The formation of a free radical is termed initiation, one of a series of reactions in which free radicals may participate. Free radical reactions can proceed further via free radical intermediates, termed propagation reactions, wherein cellular damage can occur. These propagation reactions can continue indefinitely or can be terminated by a
variety of free radical scavenging species, some of which are essential to cellular integrity and if depleted can lead to cytotoxicity.

Free radical reactions are critical for the normal operation of a wide spectrum of biologic processes. Free radicals are generated \textit{in vivo} as byproducts of normal metabolism. They are also produced when an organism is exposed to ionizing radiation to drugs capable of redox cycling or to xenobiotics that can form free radical metabolites \textit{in situ} (Freeman and Crapo, 1982). These xenobiotics either already exist as free radicals or are converted to radical species by intracellular metabolic and detoxication processes. Certain cellular metabolic states such as hyperoxia, ischemia or antibiotic therapy can favor free radical production in excess of basal rates.

Formation of OH$^-$ and H$_2$O$_2$ accounts for many of the effects of O$_2$~ generating systems, since hydroxyl radical scavengers, in addition to Superoxide dismutase (SOD) and Catalase, can protect free radical targets in many \textit{in vitro} and \textit{in vivo} test systems. Peroxisomal Catalase is the enzyme that normally metabolizes most of the H$_2$O$_2$ generated by peroxisomal oxidases.

The plasma membrane is a critical site of free radical reactions for several reasons. Extracellularly generated free radicals must cross the
plasma membrane before reacting with other cell components and may initiate toxic reactions at the membrane. Increased membrane permeability caused by lipid peroxidation or oxidation of structurally important proteins can cause a breakdown of transmembrane ion gradients, loss of secretory functions and inhibition of integrated cellular metabolic processes.

Loss of cell membrane unsaturated fatty acids, formation of lipid peroxides and oxygen uptake by lipid preparations all indicate peroxidation. Peroxidation of fatty acids containing three or more double bonds will produce malondialdehyde. The presence of this oxidation by-product can be measured with thiobarbituric acid which, although not a specific or quantitative indicator of fatty acid oxidation, correlates with the extent of lipid peroxidation. The thiobarbituric acid reaction, critically discussed by Donato (1981), needs to be cautiously interpreted because acidic reaction conditions cause thiobarbituric acid to react with sugars and lipid peroxides, in addition to malondialdehyde. To further complicate matters, malondialdehyde is a volatile product that is metabolized in vivo and will react with other cell lipids and proteins.

Hydrogen peroxide, much less reactive than OH⁻ and O₂⁻, is maintained under normal conditions at concentrations of 10⁻⁷ to 10⁻⁹ M by intracellular Catalase and peroxidases (Oshino et al., 1973). Hydrogen
peroxide has been shown to diffuse across mitochondrial membranes (Turrens et al., 1982), peroxisomal membranes (Chance et al., 1979; Jones et al., 1981) and across the plasma membrane (Schroy and Baiglow, 1981; Wang and Nixon, 1978), thus potentially exerting toxic effects at a distance from its site of generation.

Catalase has a greater activity toward H$_2$O$_2$ at higher H$_2$O$_2$ concentrations (Chance et al., 1979). Thus, cells may avoid GSH depletion and GSSG accumulation by depending more on Catalase during increased rates of cellular H$_2$O$_2$ production. More direct studies of this inter enzyme co-operativity have been reported using isolated hepatocytes, in which either peroxisomal or endoplasmic reticular H$_2$O$_2$ production was stimulated by selective addition of H$_2$O$_2$-generating substrates or by addition of H$_2$O$_2$ (Jones et al., 1981; Jones, 1982). The results supported the hypothesis that Catalase function increases as the rate of H$_2$O$_2$ production is enhanced.

Free radicals affect virtually all aspects of biologic existence by reaction with and modification of structural, metabolic and genetic material. Protective mechanisms have evolved to defend cell components from free radical damage, but disease states, xenobiotics and other environmental stresses can overwhelm defense mechanisms and cause cytotoxicity.
Humans and other mammals have a well-developed biochemical defense system, which includes both low-molecular-weight free radical scavengers and complex enzyme systems (Kaushik and Kaur, 2003). Oxygen-derived free radicals such as superoxide anion formed by the action of NAD(P)H oxidases and Xanthine oxidase are detoxified to hydrogen peroxide by superoxide dismutase. Hydrogen peroxide is reduced to water by enzymes Catalase (CAT) or Glutathione peroxidase (GPx). Reduction of the oxidized form of Glutathione (GSSG) and regeneration of GSH is accomplished by the enzyme Glutathione reductase (GR) (Halliwell and Gutteridge, 1989). GSH is one of the important antioxidants and apart from scavenging free radicals; it also plays a role in the reduction of various disulfide linkages and maintenance of proteins in proper oxidized / reduced state (Kaplowitz and Ookhtens, 1985). In excess, free radicals damage cellular components causing lipid peroxidation, protein oxidation and oxidative DNA damage (Blake et al., 1987).

Altered activities of antioxidant defense system enzymes and the levels of free radical scavengers have been found to correlate with various physiological or pathological conditions, including stress (Ji et al., 1990; Das and Banerjee, 1993). It is well known that chronic exposure to stress leads to a series of biochemical, physiological and behavioral changes, thus, altering normal body homeostasis (Wahba and Soliman, 1992) which
may lead to the development of a variety of human pathologies (Koolhás et al., 1997).

Glutathione is the principal non-protein thiol involved in the antioxidant cellular defense. Glutathione is a ubiquitous molecule that is produced in all organs, especially in the liver. It is present virtually in all mammalian tissues. Free Glutathione is present mainly in its reduced form, which can be converted to the oxidized form during oxidative stress and can be reverted to the reduced form by the action of the enzyme Glutathione reductase (Pastore et al., 2003).

Glutathione functions in the detoxification of $\text{H}_2\text{O}_2$, other peroxides and free radicals. It also plays a role in the detoxification of a variety of xenobiotics, which interact with Glutathione and are ultimately excreted in the urine or feces in the form of mercapturic acids. Glutathione is important in the function of the central nervous system; it is notable that many patients with defects of the $\gamma$-glutamyl cycle are mentally retarded and exhibit other brain defects (Meister and Larsson, 1989).

Glutathione not only protects cell membranes from oxidative damage, but also helps to maintain the sulphydryl groups of many proteins in the reduced form, a requirement for their normal function. Irreversible cell damage supervenes when the cell is no longer able to maintain its GSH.
content (Reed and Fariss, 1994). Therefore, the measurement of the various forms of Glutathione concentrations in biological samples is important for the understanding of GSH homeostasis in health and disease.

In general, an increase in the Glutathione level of a cell makes it more resistant to certain antitumor agents and also more resistant to radiation and oxidative effects. On the other hand, therapy that decreases cellular Glutathione levels usually promotes sensitivity to certain drugs, radiation and oxygen. Of much interest, certain tumor cells that have become resistant to radiation and to some anticancer agents have been found to develop high levels of Glutathione; treatment with buthionine sulfoximine decreases the cellular Glutathione level and resensitizes these cells to anti-cancer drugs and to radiation. It is, thus, evident that modulation of the metabolism of Glutathione may provide a means to selectively destroy or protect cells (Meister, 1983; Meister,1988).

It has been well established that a decrease of GSH concentration may be associated with aging and the pathogenesis of many diseases, including rheumatoid arthritis, muscular dystrophy, amyotrophic lateral sclerosis, AIDS, Alzheimer's disease, alcoholic liver disease, cataract genesis, respiratory distress syndrome and Werner syndrome (Gambhir et al., 1997, Rahman and MacNee, 2000).
It provides reducing capacity for several reactions and plays an important role in detoxification of \( \text{H}_2\text{O}_2 \), other peroxides and free radicals; moreover, Glutathione functions in the detoxification of a variety of xenobiotics which interact with the tripeptide and are ultimately excreted in the urine or feces in the form of mercapturic acids (Hayes and McLellan, 1999).

The antioxidant function of Glutathione (GSH) depends primarily on its role as a component of the enzymatic pathway that cells developed against reactive oxygen species, consisting of GSH peroxidase and GSH reductase.

Glutathione provides a first line of defense against reactive oxygen species, as it can scavenge free radicals and reduce \( \text{H}_2\text{O}_2 \). Glutathione-dependent enzymes provide a second line of defense, as they primarily detoxify noxious by-products generated by reactive oxygen species and also help to prevent propagation of free radicals.

Through the accumulated evidence, it must be concluded that glutathione, which is strictly conserved throughout all higher forms of aerobic life, plays a key role in cellular resistance against oxidative damage, not only as a free radical scavenger, but also for its emerging role as protein-bound Glutathione.
In recent studies of intracellular generation and catabolism of \( \text{H}_2\text{O}_2 \) in liver, the functions of Catalase and Glutathione peroxidase have been related to their intracellular localizations (Jones et al., 1981; Jones, 1982). Catalase catalyzes two types of reactions which are called the catalatic reaction \((2\text{H}_2\text{O} \rightarrow \text{O}_2 + 2\text{H}_2\text{O})\) and the peroxidatic reaction \((\text{DH}_2 + \text{H}_2\text{O}_2 \rightarrow \text{D} + 2\text{H}_2\text{O})\).

The relationship of \( \text{H}_2\text{O}_2 \) metabolism to NADPH / NADP\(^+\) is important since the function of Glutathione peroxidase is related to GSSG back to GSH by the NADPH-dependent Glutathione reductase and thus would appear to control the \( \text{H}_2\text{O}_2 \)-dependent GSSG efflux (Jones et al., 1981).

The predominant two systems for decomposition of endogenously produced \( \text{H}_2\text{O}_2 \) in liver are Catalase and Glutathione peroxidase (Chance et al., 1979). The relative contributions of Catalase and Glutathione peroxidase in decomposition of endogenously generated \( \text{H}_2\text{O}_2 \) are determined largely by the sub cellular localizations of the enzymes in liver cells.

In studies of \( \text{H}_2\text{O}_2 \) metabolism by erythrocytes (which contain no obvious intracellular partitioning of Glutathione peroxidase and Catalase) Cohen and Hochstein (1963) and Nicolls (1972) (cf: Jones et al., 1981), concluded that at low \( \text{H}_2\text{O}_2 \) generation rates, Glutathione peroxidase
plays a principal role in $\text{H}_2\text{O}_2$ metabolism. At higher rates of $\text{H}_2\text{O}_2$ generation, the role of Catalase becomes more important.

The relative contribution of CAT and GPx in decomposition of endogenously generated $\text{H}_2\text{O}_2$ is determined largely by the subcellular localization of the enzymes in liver cells.

There is mounting evidence that the cytotoxicity of certain antitumor compounds and xenobiotic compounds is due to reduced oxygen species produced during redox cycling (Lorentzen and Tso, 1977; Fridovich and Hassan, 1979; Lorentzen et al., 1979; Hassan and Fridovich, 1979). Oxygen cytotoxicity is held in check by the delicate balance between the rates of generation of reduced oxygen species and the rate of their removal by the different defensive mechanisms (Fridovich, 1978); any shift in this delicate balance can lead to cellular damage. Living cells have evolved different defense mechanisms to protect against the deleterious effects of the reduced oxygen species (Fridovich, 1975; Fridovich, 1978; Hassan and Fridovich, 1980).

It is known that OH$^-$ is responsible for approximately 90% of the DNA damage induced in vitro by ionizing radiation. Hydrogen peroxide has also been shown to cause DNA strand breakage and liberation of DNA bases, as well as chemical alterations of the bases. More recently, in vitro
studies have shown that $O_2^-$-generating systems cause single-strand scissions in DNA and that Superoxide dismutase, Catalase or scavengers of OH· protect against these scissions. Oxygen free radicals have also been shown to induce oxidative modifications of DNA bases [(Rhaese and Freese, 1968; Dodge, 1971; Massie et al., 1972; Armel et al., 1977; Leska et al., 1980; Brawn and Fridovich, 1981; Sharma and Yamamoto, 1980) cf: Moody and Hassan, 1982].

It is clear that oxygen free radicals can damage DNA. However, it is not known to what extent such oxidative damage or modifications of the DNA are repairable. DNA damage may lead to cell death or to mutations. Modified DNA or damaged DNA may lead to mutations by a direct alteration of the genetic code (misreplication) or by an error during DNA repair (misrepair). It seems logical to expect that the rate of formation and accumulation of modified or damaged DNA will depend both on the activities of the different protective mechanisms naturally present in the cells (i.e., Superoxide dismutase, Catalase, antioxidants) and on the capacity of the cells to repair damaged DNA (Moody and Hassan, 1982).

Though a number of alkylating agents from natural products, anti-androgens and miscellaneous agents are in use, a very few of them have been analyzed for their genetic and biochemical impact on the organisms. In the present program, alkylating agents namely, Cisplatin, Etoposide,
Flutamide and Vincristine sulphate have been tested for their various genetic and biochemical effects on Swiss albino mice, *Mus musculus*.