

**This paper is intended for Health Professionals**

## **Conventional General Pathophysiology and Treatment Principles of Cancer**

### **Conventional Medical Approach**

#### **Tumor Cell Biology**

Neoplastic disorders are the second most common cause of death in the United States. In general, a neoplastic disease consists of an altered cell population that has become unresponsive to normal controls and to the organizing influences of adjacent tissues. Plasma literally means a "thing formed". Neo means new. Therefore, neoplasms are new and abnormal formations of tissue without useful function and growing at the expense of a healthy organism. There are many types, including benign, histoid, and malignant. Malignancies have the capacity to spread locally and to distant sites, a capacity not shared with benign tumors. It is often the complications of spread that are the cause of death in cancers. There are over one hundred different kinds of cancer each of which has its own specific characteristics and, therefore, treatment.

Neoplastic disorders are defined by their biological characteristics. Certain histologic abnormalities are predictive of neoplastic biologic behavior. Histology is the study of the microscopic structure of tissues. Among the histologic abnormalities of neoplasms are a high frequency of mitotic figures, meaning that many cell nuclei are reproducing. Also there are derangements of nuclei, the vital body in the protoplasm of the cell and the essential agent in growth, metabolism, reproduction, and the transmission of characteristics of a cell. At the same time that these abnormalities in the cell are taking place, an alteration is also taking place in the normal tissue architecture, and evidence begins to accumulate that there is an invasion of adjacent structures and possibly even distant metastatic spread.

Malignant neoplasms commonly arise in tissues with self-renewing cell systems. Self-renewing cell systems include skin, mucosal linings, blood cells, immune cells, and hormonally-responsive cells, to name a few. Normal cellular replication and maturation takes place at a fairly high frequency in these types of cells. For example, the mucosal lining of the digestive tract replaces itself approximately every twenty-four hours. Breast tissue cells respond usually on a monthly basis to hormonal influences as part of the menstrual cycle. Cancers can be seen as caricatures of normal cellular replication and maturation. It is thought that the diversity that develops in tumor cell populations probably arises from imperfect attempts at maturation. Maturation refers to a cell changing and growing towards an end goal of the climax of that type of cell within a given system. Once the cell has fulfilled its life work, whether it be some kind of immune function or the production of milk in the lacteals of the breast ducts, then it enters apoptosis, or programmed cell death.

The main biologic properties displayed by tumor cells are actually common to many normal cells within the body. For example, lymphocytes, granulocytes and macrophages are all immune cells that move to distant sites in the body and "invade" tissues as part of their normal functioning. During embryogenesis various cells move to distant sites, implant, and develop within new organs and tissues. Many of the phenotypic markers found on cancer cells are also present in immature normal cells. These include carcinoembryonic antigen or CEA,  $\alpha$ -fetoprotein, and fetal isozymes. One could say that normal cells contain genetic information for cancer-like traits and that cancerous cells are cells that once were normal but were injured in such a way that a mutation occurred and they have been trying to get back home ever since.

There are also chromosomal changes that are associated with cancer, and because of this many neoplastic disorders are characterized by specific karyotypic abnormalities. A karyotype refers to the systematic array of the chromosomes of a given cell in the metaphase stage. The chromosome is a microscopic body which develops from the nuclear material of a cell and is especially conspicuous during mitosis or cell division. Chromosomes contain the genes, the hereditary determiners. These numbers are stable for a species; the number for humans is 46, or 23 in all somatic cells. These constitute the diploid number. The ovum and sperm each contain 23, or one each of the 23 pairs. Therefore, when a diagnosis of acute leukemia, for example, is given, very often a genetic abnormality is found at the monosomy 5 and 7 gene sites. An abnormality is often found at the 3p site in small cell cancer of the lung. Chromosome 8 is translocated in Burkitt's lymphoma, and so on. In fact, locating these abnormalities is often part of the histological diagnosis for a cancer. These markers are also used as targets in modern gene therapy for some kinds of cancers.

Genes that have been frequently found to be associated with cancer pathogenesis are called oncogenes. Cells expressing mutated forms of these genes have a high probability of progressing to malignancy. The normal genes before being "switched on" are called proto-oncogenes. The mutated forms are called oncogenes, and are said to be activated. These genes are denoted by 3-letter names, such as sis, ras, and myc. Since many of the oncogenes were first discovered as mutated cellular genes incorporated into the nucleic acid of RNA tumor viruses, the activated forms are denoted v-onc as in v-sis and the proto-oncogenes are c-onc as in c-sis. Arguments have been advanced that support qualitative and quantitative abnormalities of oncogene expression as key to the process of tumorigenesis. Cellular DNA sequences have a high degree of similarity in structure and in origin to the known transforming sequences of retroviruses. There is currently a great deal of study in this realm because these genes are highly conserved in nature and are found in a large number of animal species. It is possible that they play a role in normal growth and development and when injured in some way, therefore, contribute to abnormal growth processes. To date approximately 25 oncogenes have been identified.

Proto-oncogenes code for proteins involved in the receptor-activated proliferation/differentiation pathways. Proto-oncogenes are classified into four groups:

1. **Growth factors** which stimulate cell signaling, such as platelet-derived growth factors.

2. **Growth-factor receptors** which receive oncogenic information. Many growth-factor receptors contain tyrosine kinase activity, e.g., erbB-2 protein, which is found in more aggressive forms of breast cancer.

3. **Signal transducers** which are components of the intracellular signaling pathways. Signals are transmitted from cell-membrane receptors to the nucleus by second messengers. Cascades of protein kinases are involved in mediating these signals by way of proto-oncogenes. The ras gene plays a role here. Cyclin-dependent kinases (CDK's) are involved in many cancers. CDK-1 plays a role in cell division and a role in 90% of all breast cancers. Its presence facilitates the proliferation of vascular endothelial cells. These cells form the basis for the creation of new vessels that feed tumors (angiogenesis). Many supplement therapies and probably many Chinese herbs interact with growth factors and growth-factor receptors to limit tyrosine kinase activity and stop cell proliferation.

4. **Nuclear transcription factors** bind DNA and activate gene expression. The proto-oncogene c-sis is the gene for one form of platelet derived growth factor. The oncogene, v-sis, causes fibroblasts to proliferate because, whereas the normal cellular sis gene, c-sis, is repressed in fibroblasts, the viral copy, v-sis, is under the control of the active viral regulatory region and is highly expressed. Thus, the cell makes its own growth factor and grows continuously.

One growth factor gene is c-erbB. Normal receptor activation triggers the extensive network of reactions which culminate in mitosis. The mutated gene, v-erbB, activates this cascade without the normally present EGF, a polypeptide growth factor, and a cell with this mutated receptor is continuously stimulated to grow. The erbB-2 (probably a hormone receptor) is a gene expression that is frequently amplified in breast cancer. The erbB-2 is an example of a proto-oncogene with a point mutation or translocation. The her-2neu oncogene is related to erbB-2, and a newer form of chemotherapy for her-2neu positive breast tumors, called Herceptin, is an example where the concept of oncogene expression is utilized in anti-neoplastic therapy.

Another commonly linked proto-oncogene is the c-myc protein which probably has to do with regulatory rates in cell growth. Mutations in the v-myc gene cause increased expression and, therefore, persistent proliferation. In cancers, it is important to note that proliferation per se is not necessarily abnormal but the differentiation to terminal or mature cells is abnormal, delayed or absent in the malignant clone of the original normal cell.

**Tumor-suppressor genes** are active genes that suppress the formation of tumors. They are a normal part of the body's immune system. Tumor-suppressor genes can be "knocked out" through inheritance which gives the individual a predisposition to develop cancer. They can also be knocked out by other as yet unknown means. It seems probable that exposures to toxic chemicals may have a negative effect on the functioning of tumor-suppressor genes. These genes are regulators that control the expression of other genes. The most common gene

mutation is in the tumor-suppressor gene p53. Many cancers are the result of a defect in the p53 gene. For example, 70% of all colo-rectal cancers, 30% of all breast cancers, 50% of all ovarian cancers, and all small-cell lung cancers have defects in the p53 tumor-suppressor genes. The flavone quercetin, found in brassicas ( broccoli, cauliflower, kale, brussel sprouts ) helps to prevent a defect in this gene.

**Oncoviruses** are a cause of insertional mutagenesis which occurs when cells are infected by viral genes. This causes mutation to already existing DNA. Epstein-Barr virus ( EBV ) is linked to esophageal cancer and one type of lymphoma. Herpes Simplex virus ( HSV ) and human papilloma virus ( HPV ) are linked to cervical cancer. Hepatitis B and C are linked to hepato-cellular cancer.

There are 63 trillion cells in the body each of which undergoes 5000 mutations in a day. It is amazing that more malignancies do not occur when viewed from this perspective. Mutation occurs when there is a build-up of oxidative damage whereby the gene itself is altered and then initiates the process of malignancy. The protective mechanisms within the body to prevent malignancy from occurring as a result of mutation include:

- inhibition of mutation by reducing the overall number of mutational changes
- repair of mutations that do occur
- and inhibition of an occurrence by turning off a damaged cell so that it cannot proliferate

## **Apparent Causal Factors**

Epidemiological studies have identified environmental hazards, social practices, and heritable factors that seem responsible for many cancers. Because there is often a prolonged period of development into a cancer the precise etiological agents responsible are sometimes difficult to ascertain. Many cancers are multi-factorial . The identification of cause for specific cancers and, therefore, prevention as a primary means of treatment has never been the primary focus of those governmental agencies and research institutes whose mandate it is to fight cancer. This is an area of great frustration among families who have lost loved ones to cancer and among those who treat cancers on a daily basis.

There do seem to be clearly increased incidences of neoplastic diseases within certain families but a clearly defined pattern of inheritance is established only rarely. Retinoblastoma, lipomatosis, colonic polyposis amy present in families with a pattern of dominant inheritance. Also multiple endocrine neoplasm syndromes involving the pituitary, thyroid, and pancreatic islet cells follows a dominant inheritance pattern in some cases. However, for the most part, the chromosomal instability syndromes and immunodeficiency disorders are transmitted as autosomal recessive characteristics making patterns difficult to identify.

The relative incidence of various cancers relative to age, gender, and other constitutional factors indicates that other determinants do exist. For example, acute lymphocytic leukemia is essentially a disease of childhood. Malignant melanoma is a post-pubertal phenomenon. Testicular tumors and Hodgkin's disease are most frequently diseases of young adults. Breast cancer is far more common in women than in men. Other kinds of cancer like chronic leukemias, myeloma, and many solid tumors have increasing rates of incidence with age.

Acquired clinical disorders that are not neoplastic are often associated with increased incidence of malignant tumors. Usually these tumors arise from tissue that has been undergoing prolonged regenerative activity. Maybe the increased rate of cellular proliferation enhances the possibility for and development of a neoplasia. For example, Bowen's disease of the skin tends to evolve into a squamous cell cancer. Non-familial polyps are regarded as precursors for malignant lesions. Human papilloma virus of certain types is considered causative for cervical cancer.

The number of chemicals introduced for the first time on earth has climbed astronomically since the 1940's. Of the approximately 85,000 new chemicals introduced since that time only about 1500 have been tested for carcinogenicity. The combinations of various new chemicals have also not been tested. New more sophisticated techniques for measuring the levels of 150 chemicals stored in human body tissue show that most people by the age of 60 are carrying at least 80 chemicals in various body tissues. The carcinogenicity of these chemicals is untested, as is their contribution to other diseases. Petroleum-based chemicals, especially organochlorines used in the monocultural agribusiness industry, are especially problematic. Organochlorines are used to make pesticides and certain chemical fertilizers. Organochlorines persist in the environment, some for thousands of years. They accumulate downstream or downwind from their original application area sometimes up to one million times the amount of the original application. They are fat soluble and when ingested accumulate and can act in many ways ( xenoestrogenically ) to cause and promote cancers. The Israeli's eliminated only one organochlorine pesticide from their agricultural use and in ten years the breast cancers rates in Israel dropped by 30%. This is only one example of a chemical used ubiquitously in agriculture can effect human health.

Viruses have been shown to be oncogenic in several animal species. At least twelve strains of human adenoviruses are capable of inducing tumors in newborn laboratory animals. HPV is linked to papillomas; EBV is linked to Burkitt's lymphoma and esophageal cancer; HSVII has been associated, along with HPV, with cervical cancer; a retrovirus has been associated with aggressive T-cell leukemia-lymphoma; HCV has been linked to liver cancer, and so on.

Serologic studies have identified tumor-related antigens in patients with leukemia, osteogenic sarcoma, melanoma, and other soft tissue sarcomas. Similar antibodies have been found in family members. This implies a possible link with a virus or other infectious agent and tumor pathogenesis. It also implies that unrecognized infections in normal individuals may be responsible for some cancers. Hepatitis C and HPV are the most obvious examples.

Antigens are substances that induce the formation of antibodies; antibodies are protein substances developed by the body, usually in response to the presence of an antigen. Normal antibodies are also present in the circulation and may be transferred by the mother in utero or may be developed during life by subclinical contact with the disease-producing agent, thereby providing immunity to diseases. For example, there is distinct antigenicity associated with Burkitt's lymphoma, nasopharyngeal cancer, melanoma, and neuroblastoma among others. Fetal antigens have been demonstrated in cancer of the colon, pancreas, and lung (CEA). And a-fetoprotein is associated with hepatoma and embryonal carcinoma and testicular cancer. CEA is also present in the blood of pregnant women, heavy smokers, and in some patients with hepatic cirrhosis, pulmonary emphysema, and ulcerative colitis.

There is a defined humoral and cell-mediated response to tumor-related antigens. And sensitized lymphocytes can be prevented from acting against tumor cells by the presence of "blocking or enhancing antibodies". Immunologic responsiveness to tumor antigens may be thwarted by the presence of suppressor T cells, large amounts of tumor (immune paralysis), or tolerance due to the introduction of tumor antigen very early in life. The role of immunologic surveillance and tumorigenesis is an area requiring much investigation.

### **Common Modes of Clinical Presentation**

Neoplastic diseases present themselves in various and inconstant ways. The onset of a neoplasm is difficult to date. Even when there is a known exposure to a carcinogen, a prolonged latent or induction period is common before clinically detectable disease evolves. For example, in a ductal carcinoma of the breast it generally takes seven to ten years for a neoplastic tumor to develop into a one centimeter tumor which is just barely palpable.

Carcinoma-in-situ is considered a premalignant lesion. The most common site for this earliest stage of a cancer is the uterine cervix. Many non-invasive lesions like this do not develop into cancer. Often the biopsy procedure will remove the entire in situ; this the diagnostic technique also becomes the treatment technique. Ductal carcinoma in situ (DCIS) in breast cancer are also in this realm and the lumpectomy surgical biopsy procedure can be curative (although radiation to the site is often performed as added insurance).

Malignant neoplastic diseases may exist in a human for months and even years and remain asymptomatic. Often their presence is found through routine screening for either cancer or for general health. Prostate cancer can fall into this realm as well as cervical and breast cancers. Prostate cancer is sometimes so indolent that it is only on autopsy that it is found. Another example is chronic lymphocytic leukemia which may exist for long periods without symptoms.

Usually in non-leukemic neoplasms the presentation of the patient relates to problems arising from physical alterations in adjacent organ systems. Findings often include: the presence of an

obvious tumor mass; the presence of an ulcerative lesion that will not heal; chronic bleeding and the results of blood loss; bone destruction; involvement of the central or peripheral nervous system with resultant seizures, paralysis, and pain; acute or chronic obstruction of a hollow organ, e.g. the lungs, colon, stomach, gallbladder, urinary bladder; obstruction of mediastinal structures. When mass lesions are present the initial presentation may be in relation to a distant site from the origin of the cancer, as in metastatic disease. Common sites for metastatic spread are the cervical and supraclavicular lymph nodes, lungs, liver, bones, and brain.

## **Physiologic Abnormalities**

Tumor growth necessarily causes many functional abnormalities. As tumor masses enlarge they cease to grow exponentially. The cells themselves cease to proliferate and the internal cells in the tumor begin to die. One function of a tumor is to produce a blood supply for itself. Cells most distant from the blood supply begin to lose access and then die, in a sense, of malnutrition. Therefore, most tumors will have areas of necrosis. This will often set up an inflammatory response and local and possibly systemic fever. Hormonal-like substances are secreted by the tumor to induce angiogenesis. These substances may also play a role in metastatic spread. In addition, many tumor cells appear to differentiate to terminal or mature cells that no longer grow. It is hypothesized that some tumor cells may accumulate so much genetic damage that they die, in a sense, of self-inflicted wounds.

All of the above abnormalities cause various functional derangements. Tumors may arise in organs that normally produce physiologically active substances, such as hormones. If the normal feedback mechanisms are interrupted by a tumor obstruction or by substances the tumor is putting off, then characteristic clinical illnesses will result. Pituitary tumors are an example; when hormonal imbalances relative to pituitary output are seen this leads the clinician to the gland itself and eventually to a diagnosis. More commonly, neoplasms produce substances that induce inappropriate secretion of normal hormones. Tumor cells generally try to differentiate along lines similar to those of the cell populations from which they arose. The abnormality of their genetic material makes this impossible and so normal processes are, especially in self-renewing systems, interfered with usually in the direction of a hyper-reaction.

## **Diagnosis of Cancer**

The summary of a cancer diagnosis will include an anatomical or clinical diagnosis and a histologic/cytological diagnosis. These areas are combined in arriving at a diagnosis and prognosis which then leads the physician or team to develop a treatment plan.

Methods of definitive diagnosis include:

- surgical biopsy with tissue examination to give a clear picture of the extent of the tumor

- examination of tumor cells under a microscope to define the extent of the abnormality
- examination of tissue and cells obtained by fine needle aspiration or biopsy

The parameters of the above investigations include several arenas.

### **Tumor Size**

There is often a direct correlation between tumor size and the risk of recurrence. Although this will vary depending on the type and location of the primary tumor, generally the larger the tumor the greater the risk of recurrence.

### **Nuclear/histologic Grade**

The nuclear or histologic grade refers to the degree of cell differentiation within a tumor and is based on the pathologist's assessment of each cell's nuclear size and shape in the biopsy sample. It also refers to the number of mitoses ( cell divisions ), and the degree of tubule formation. Tumors of low malignancy are graded 1 and are associated with the best prognosis. Grade 3 tumors are associated with the worst prognosis. Cells that are well-differentiated imply less mutation; those that are not differentiated, each looking different from the cell next to it, have probably been running amuck for a longer period of time.

### **S-phase Fraction and DNA Ploidy**

Flow cytometry measures both DNA ploidy ( DNA content ) and the S-phase fraction ( the fraction of cells actively cycling or synthesizing DNA ). Aneuploid tumors ( the cells in the tumor contain an abnormal number of chromosomes ) with a high percentage of cells in S-phase are more likely to recur than are tumors with a low S-phase fraction. These measurements measure the aggressiveness of a tumor and this means the degree to which it is proliferating based on the genetic action of the tumor cells.

**Fine needle aspiration or FNA** is used extensively in the diagnosis of many tumors including benign tumors. It involves the insertion of a hypodermic needle into the core of the tumor and aspirating tissue and cells for later analysis under a microscope. It provides a rapid diagnosis since results can usually be gotten during the same day. False-negative can occur when a small mass has few cancer cells and they have not been picked up during the procedure.

**Open biopsy** is a common procedure for diagnosis. In smaller tumors this procedure may become the treatment as well; this is especially true in small ductal carcinomas of the breast. It is important in this technique that the margins around the excised tissue be completely free of cancerous tissue. If the margins are not clear or end up being very close to the lesion ( less than 8mm ), this becomes a problem in terms of spread and a lack of clarity regarding the remaining tissue. Often these excisional biopsies are done on an outpatient basis under local anesthesia depending on the location of the tumor. Many breast cancers are diagnosed in this way; liver biopsies, on the other hand, are done in the hospital.

Sometimes in non-palpable lesions where microcalcifications are present ( as is often true in

breast cancers, for example ) another FNA technique is utilized called **stereotaxic needle localization**. This is accomplished by inserting a hooked wire into or adjacent to the lesion. Methylene blue is injected as a precaution against the needle becoming dislodged. The excisional biopsy is then performed with the wire in place as a marker for deep and non-palpable microcalcifications found earlier, e.g. in mammography.

**Routine studies** are also done often including a chest x-ray to rule out metastatic disease in the lung or mediastinum. Also x-ray or ultrasound may be done to other parts of the body including the abdomen and skeletal structures. Or a bone scan may be done particularly if the presentation is late and there is musculoskeletal pain. Blood testing will be done to look at liver function, hematopoietic abnormalities, and in some cases hormone levels.

## Staging

Clinical staging includes physical examination, with careful inspection and palpation of the skin, the effected area, the local and regional lymph nodes. It also includes a pathologic examination of the tissue and any imaging done to establish the diagnosis. Operative findings are elements of clinical staging, including the size of the primary tumor and the level of invasion of that tumor and the presence or absence of regional or distal metastasis.

Pathologic staging includes all data used for clinical staging and surgical resection as well as pathologic examination of the primary carcinoma, including not less than excision of the primary carcinoma with no tumor in any margin of resection. If there is tumor in the margin of the resection, it is coded TX, i.e. the extent of the primary tumor cannot be assessed.

A universal system has been put in place for the staging of cancers. There are also individualized systems in place for certain specific tumors which will be addresses in chapters discussing those particular cancers. The current anatomic staging system, the TNM system, describes the anatomic extent of disease based on the assessment of three components:

T - the extent of the primary tumor

N - the absence or presence and extent of regional lymph node metastasis

M - the absence or presence of distant metastasis

The addition of numbers to these three components indicates the extent of malignant disease:

T0, T1, T2, T3, T4    N0, N1, N2, N3    M0, M1

This is, in effect, a shorthand system for describing the extent of a particular malignant tumor.

The staging work-up consists of all of the above procedures and assessments. It provides an anatomical, biochemical, and genetic map of the malignant disease in a given patient. It is important because it not only provides information concerning prognostic factors including

potentials for recurrence but also information concerning the therapies to be used.

## Principles of Treatment

**Surgery** is the primary defense against any solid tumor. The purpose of surgery is to remove local and regional disease. When there is no metastasis surgery may be curative.

Radiation therapy is being used more and more for particular types of tumors. It is used in various delivery mechanisms for many situations in which residual tumor cells are a concern or where either the staging is too late for surgical resection and there is no adequate chemotherapy as a stand alone therapy. External beam radiation therapy is used in many solid tumor cancers and in some blood and lymph cancers. High-energy irradiation delivered by a linear accelerator is preferable to older cobalt-60 irradiation when using external beam irradiation. The therapy is usually 5 days per week for 6 to 7 weeks as a course. Seed implants are also used most commonly in prostate cancer. A treatment simulator is now considered extremely desirable, and computerized planning is essential. Cautions in radiation therapy are pre-existing autoimmune disease because the inflammatory components of these diseases are exacerbated by radiation, pre-existing pulmonary or cardiac disease. Collagen vascular disease and uncontrolled diabetes are also probable contraindications for radiation therapy.

Concomitant radiation therapy and chemotherapy increase local tissue reaction and can cause greater damage. Therefore, radiation is often delayed until the end of chemotherapy in some cases provided the delay is not longer than six months. Delaying radiotherapy may result in an increase of local failure of treatment. However, there are some cases in which radiation may be done first or concurrently with chemotherapy.

In advanced solid tumor cancer where surgery is no longer an option, radiation therapy can be used to consolidate or shrink a tumor in order to make it resectable. The aim may also be to control local disease in a non-resectable tumor. Here full-dose radiation is used and is sometimes supplemented by interstitial implantation of radioactive isotopes or seeds. In late disease, radiation is used to treat distant metastasis especially to the bone and brain.

**Chemotherapy and hormonal therapies** are considered systemic adjuvant treatments for many cancers. The purpose of adjuvant therapy is to treat micrometastatic disease before it is clinically detectable in the hope that the small tumor burden will be easier to eliminate. Patients at high risk for developing metastatic disease are treated after their primary tumor is treated. Chemotherapy and hormonal therapies have been used as adjuvant therapy. The term adjuvant refers to treatment used in addition to and following primary treatment in order to cure, reduce, control, or palliate the cancer. The term neoadjuvant refers to therapy given before the primary treatment in order to shrink or otherwise effect the tumor.

Chemotherapies have many groupings based on the cytotoxic action of the drug. They are generally grouped as vesicants or irritants. Vesicants are agents that cause blistering. Irritants produce a local inflammatory reaction. These main groups are then broken down further into several sub-categories: a) alkylating agents like the platinum, Cisplatin; b) antibiotic agents like Adriamycin; c) DNA intercalators like Herceptin; d) Vinca alkaloids like Vincristine; e) epipodophyllotoxins like Etoposide; f) hormonal agents like Tamoxifen; g) enzymatic agents like Asparaginase; h) antimetabolites like Cytarabine. Podophyllotoxins are made from the rhizome of *Podophyllum peltatum* and are used as a caustic. Many cytotoxic chemotherapeutic drugs were initially made from plant materials.

Non-cross-resistant therapies are combinations of multiple non-cross-resistant drugs evolving out of a rationale that the presence of subsets of cells resistant to certain drugs require multi-pronged approaches. The treatment principle is not unlike that for HIV infection. These combinations are given acronyms that can become extremely confusing. Many PDRs or oncology texts have a list of acronyms in their addendums. Examples are: CMF which is the acronym for Cytoxan, Methotrexate, and Fluorouracil; CFP is the acronym for Cytoxan, Fluorouracil, and Prednisone. Some acronyms include combined references to generic drugs and brand name drugs, making things even more confusing.

Hormonal or endocrine therapies are used to treat tumors that are associated with tissue that is, under normal circumstances, responsive to specific hormonal substances. Testosterone, progestins, antiadrenal drugs, and prednisone are commonly used hormonal substances used to interact with or interfere with the proliferation of cells in specific types of tissue. Examples are the use of estrogen therapy in prostate cancer (Lupron), and the use of anti-estrogenic therapy (Tamoxifen) in estrogen receptive breast tumors. Sometimes endocrine agents are used for up to five years after initial diagnosis whereas chemotherapies are most commonly used for one to two years.

## **Biological Therapies**

Biological therapies include different biological agents like BCG (bacillus Calmette Guerin), levamisole, polyA-polyU, *Corynebacterium parvum*, Azimexon, Basidio p.p., interferon, interleukins.

The interferons constitute a family of naturally occurring proteins that were first recognized for their ability to confer on cells resistance to viral infection. The IFN's are designated alpha interferon, beta interferon, and gamma interferon. The genes encoding these proteins have been sequenced and cloned. Alpha and beta interferons are class I. Two recombinant human alpha interferons are licensed for clinical use in the U.S. The broad classes of action for interferons are characterized as 1) antiviral, 2) antiproliferative, 3) regulatory of differentiation, 4) modulatory of lipid metabolism, 5) inhibitory of angiogenesis, 6) antitumoral, and 7) immunoregulatory.

All biologic activities of the IFNs require binding to specific cell-surface receptors. All IFNs

usually act in a paracrine fashion and are present in high concentrations in the circulation. Antibodies to recombinant alpha interferon are detected in two-thirds of patients receiving alpha interferon. Administration of nonrecombinant alpha interferon may restore responsiveness in patients whose disease ( including cancer ) has relapsed. It is also used in CML and multiple myeloma. It has been used in Kaposi's sarcoma, Hodgkin's and low-grade non-Hodgkin's lymphomas. It can be used in combination with combination chemotherapies.

**Interleukin -2** is from a family of polypeptides that mediate interactions between leukocytes. It was initially called T-cell growth factor. It stimulates proliferation and enhances function of other T-cells, NK cells and B-cells. IL-2- activated B-cells generate secretory rather than membrane-associated IgM, and macrophages gain cytolitic maturation and elaborate transforming growth factor-beta ( TGF-beta ) when stimulated with IL-2. These immunomodulatory effects are the rationale for studying IL-2 as an anti-cancer agent. Its toxicity has hindered widespread implementation. Anemia, thrombocytopenia, endothelial cell damage, renal damage are all factors that need to be overcome. IL-2 has been used in treatment for renal cell carcinoma and metastatic melanoma.

**Hematopoietic growth factors** are a family of glycoproteins with important regulatory functions in the processes of proliferation, differentiation, and functional activation of hematopoietic progenitors and mature blood cells. They include erythropoietic, colony stimulating factors, various interleukins, stem cell factor, thrombopoietin, and flt-3/flk-2, a growth factor of early progenitor cells. The CSF's ( colony stimulating factors ) include granulocyte CSF ( G-CSF, filgrastim ( Neupogen ) ), granulocyte-macrophage CSF ( GM-CSF, sarramostim ( Leukine ) ), multipotential CSF ( multi-CSF, also known as IL-3 ), and monocyte macrophage CSF ( M-CSF, also known as CSF-1 ).

These growth factors interact at various levels of the hematopoietic differentiation cascade. They are present and produce growth factors at multiple sites in the body. They are used for amelioration of myelosuppression after chemotherapy and allow for dose escalation of toxic chemotherapeutic drugs by rescuing the patient from severe neutropenia. They are used in autologous bone marrow transplantation in the same way. And in myelodysplastic syndromes that are iatrogenic treatment-related neoplastic clonal stem cell disorders caused by toxic treatment IL-3,4,5 plus GM-CSF and G-CSF have been studied. Some are positive and some are not. G-CSF is commonly used as rescue therapy during and after chemotherapy in many cancers.

**Retinoids** are substances structurally or functionally related to vitamin A, or retinol. They reportedly induce differentiation and/or suppression of proliferation of many cell lines, including embryonal carcinoma, leukemia, melanoma, neuroblastoma, and breast carcinoma. Synergy has been seen when retinoids are combined with vitamin D and its analogs ( like vitamin D3 ), as well as in combination with other cytokines. These have been used most commonly to reverse or suppress carcinogenic progression to invasive cancer. Also there have been studies that show in acute promyelocytic leukemia ( APL ), All-trans retinoic acid ( ATRA ) has been used to

achieve complete remission. Retinoids are highly teratogenic and must be used with extreme caution in women of child-bearing age. RAS, or retinoic acid syndrome, is seen in up to 20% of patients with APL and treated with ATRA. It manifests as fever, respiratory distress, hyperleukocytosis, edema, pericardial effusions, hypotension, and renal failure.

Monoclonal antibodies ( MoAbs ) are antibodies that are capable of binding with high affinity to specific determinants. They have the advantage of directly neutralizing a target, indirectly mediating immune damage by means of complement activation, and activating cellular cytotoxicity by other immunocompetent cells. Many MoAbs have been conjugated with other agents that are cytotoxic, including chemotherapy. They may have the potential to improve targeted cell therapy. They are also used to target growth-factor receptors.