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ANTI-CANCER ACTIVITY OF COW URINE: CURRENT STATUS AND FUTURE DIRECTIONS

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Abstract

Cow urine has a unique place in Ayurveda and has been described in 'Sushrita Samhita' and 'Ashtanga Sangraha' to be the most effective substance/secretion of animal origin with innumerable therapeutic values. It has been recognized as water of life or "Amrita" (beverages of immotality), the nector of the God. In India, drinking of cow urine has been practiced for thousands of years. It is an important ingredient of panchgavya, a term used to describe five major substances (urine, milk, ghee, curd and dung), obtained from cow. All the five products possess medicinal properties, and are used singly or in combination with some other herbs against many diseases, even those not curable by allopathic treatments. This kind of alternative treatment, termed as 'panchgavya therapy' or 'cowpathy', has been reported to be beneficial even for dreaded diseases like cancer, AIDS and diabetes. Practitioners of Ayurvedic medicine from India routinely use cow urine as a remedy and the medicines made from it are used to cure several diseases. Improvements have been shown or reported with those suffering from flu, allergies, colds, rheumatoid arthritis, bacterial/viral infections, tuberculosis, chicken pox, hepatitis, leucorrhoea, leprosy, ulcer, heart disease, asthma, skin infections, aging, chemical intoxication etc. Cow urine can kill the number of drug resistant bacteria and viruses. Recently the cow urine has been granted U.S. Patents (No. 6896907 and 6,410,059) for its medicinal properties, particularly for its use along with antibiotics for the control of bacterial infection and fight against cancers. Through extensive research studies a cow urine distillate fraction, popularly known as 'ark', has been identified as a bioenhancer of the activities of commonly used antibiotics, anti-fungal and anti-cancer drugs. Thus it can promote and augment the bioactivity or bioavailability or the uptake of drugs in combination therapy and reduce the dose and duration of treatment. These milestone achievements highlight the beneficial role of cow urine in treating bacterial infections and cancers and that cow urine enhances the efficacy and potency of therapeutic drugs. During the past few years cow urine therapy has provided promising and authentic results for the treatment of cancer, a deadly malady which is being faced by the mankind and the incidences of which are ever increasing in the current scenario of changed lifestyle and food habbits along with exposure to predisposing factors of carcinogens such as tobacco chewing, smoking, alcohol intake, environmental pollutants, occupational health hazards etc. Anti-cancer potential of cow urine therapy has been reflected by several case reports, success stories and practical feed back of patients for the treatment of cancer. Cow urine enhances the immunocompetence and improves general health of an individual; prevent the free radicals formation and act as anti-aging factor; reduces apoptosis in lymphocytes and helps them to survive; and efficiently repairs the damaged DNA, thus is effective for the cancer therapy. Experimentally it has been proved that among all sorts of urines, the urine of the Indian cows is most effective. Seeing the potential use of indigenous cow urine in several ailments including even the cancer, the use of Gomutra (cow urine) of indigenous breeds of cattle should be promoted extensively. However, scientific validation of cow urine therapy is required for its worldwide acceptance and popularity. This review highlights the anti-cancer activity of cow urine and the strategies for promoting its vital medicinal potential and prospectives for the benefit of mankind with the view that cow urine therapy needs immediate attention, promotion, and wide popularity and proper support of the scientists, researchers and clinicians to strengthen this alternate low cost therapy having no side effects, as generally observed with chemotherapy and radiation therapy being followed for curing cancers, and thus inspire confidence in the public about its good virtues.

Key words: Cow urine, cancer, tumor, cowpathy, panchgavya, treatment

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INTRODUCTION

"Panchagavya" is a combination of cow urine, milk, dung, ghee and curd. Indian cow breeds are unique and distinct species, popularly known as "Kamdhenu" and "Gaumata, has high socio-cultural values, plays significant role in rural economy, represent cattle wealth and bio-diversity. The ancient Indian system of medicine, Ayurveda, has detail mentions of importance of panchgavya in the treatment of various human diseases. Apart from high medicinal values, panchgavya has many beneficial implications in agriculture, organic farming as good quality natural manure and biopesticides, bio-fertilizer, pest repellants and as alternate energy resources (biogas, fuel and electricity) (Charaka-Samhita, 1981, Susruta Samhita, 1985; Tietze, 1996; Chauhan, 2000, 2001, 2002 a,b, 2004a,b, 2005; Fulzele *et al.,* 2001, 2003; Joshi, 2002; Nautiyal, 2002; Garg and Chauhan, 2003a,b; Achliya *et al.,* 2004; Saxena *et al.,* 2004, Singh and Chauhan, 2004, Dhama *et al.,* 2005). These can provide food free from health hazards of chemical fertilizers and pesticides. Scientists / clinicians are facing problem in modern allopathic treatments due to the development of multiple drug resistance in microorganisms, presence of antibiotic residues in food chain and/or associated allergies and autoimmune disorders in humans. Immunity is reducing drastically as a result of the environmental pollution, use of agrochemicals in agriculture and presence of pesticides, heavy metals, fungal toxins etc. in the food chain. This has lead to the inefficacy of antibiotic drugs, development of resistance in bacteria, recurrent infections, and/or decreased immune status of an individual. As per WHO, the twentieth century wonder drugs "antibiotics" will not remain useful and become almost ineffective by the year 2020. Also the incidences of human sufferings from cancer, a deadly malady, are ever increasing in the current scenario of changed lifestyle and food habbits along with dangers of carcinogen in the form of tobacco chewing, smoking, alcohol intake, environmental pollutants, occupational health hazards etc. The methodologies like chemotherapy, radiotherapy and surgery are available for treating the cancer, but the success rate is low particularly with malignant tumors, and moreover, these therapies produce severe side effects adding to the physical and mental agony of the patient and are costly, and even some of the tumors are incurable. In all these circumstances mentioned above one has to think over the alternative therapeutic approaches to control the infections, save mankind from different ailments and fight diseases such as cancer (Garg and Chauhan, 2003; Chauhan, 2005).

Utilizing the beneficial properties of cow's urine, milk, ghee, curd and dung, the kind of treatment is called panchgavya therapy or **cowpathy**, a system of naturopathy. Panchgavya products have been found to be beneficial in curing several human ailments and enhance the body's immunity and resistance to fight the infections. This kind of alternative treatment has been reported to be beneficial even for dreaded diseases like cancer, AIDS and diabetes. Of these, the cow urine recently has received worldwide attention. Two US patents have been granted to Indian scientists on establishing the bioenhancing properties of cow urine, its use in tuberculous patients and fight cancers, thus opening a new era in medical science. Cow urine along with the antibiotics can also prevent the development of resistance in microorganisms against the antibiotics. Several scientists from different laboratories of Council of Scientific and Industrial Research (CSIR), All India Institute of Medical Sciences (AIIMS), G.B. Pant University of Agriculture and Technology, Pantnagar, and Indian Veterinary Research Institute (IVRI), besides Non-Government Organizations (NGOs) and other Institutes are working on different medicinal properties of cow urine and other panchgavya products. Several students of M.Sc., M.V.Sc., M.D. and/or Ph.D. are working on the medicinal properties of cow urine and other panchgavya products (Chauhan, 2005).

The people frustrated from the heavy medication of allopathy are now using cowpathy drugs and being benefited by the panchgavya products for several diseases. Cow urine is an important element of panchgavya, and the cow urine therapy has been successful in relieving human sufferings from flu, allergies, colds, rheumatoid arthritis, bacterial/viral infections, hepatitis, leucorrhoea, leprosy, asthma, skin infections etc. However, scientific validation of cow urine is required for its worldwide acceptance and popularity in terms of medicinal applications so as to exploit its optimal power for the service of mankind. Regardless of scientific validation, people are using and getting benefits of it. The present review focuses the anti-cancer activity of cow urine, well supported by the known scientific facts and case reports, success stories and feedback of cancer patients treated with cow urine therapy. The authors have compiled this information with ultimate goal of popularizing "Cow Urine Therapy / Chikitsa" as an alternate prophylactic / therapeutic approach, which is safer, cheaper and without any side effects for fighting cancer, the most dreaded and incurable malady. Many a good virtues of cow urine need proper attention and promotional campaigns and judicious support of the scientists, researchers and clinicians so as to strengthen

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the miraculous cow urine therapy which can inspire confidence in the physicians as well as the public that deadly diseases like cancer could be treated.

CANCER

Cancer is the term used to describe the uncontrolled growth of abnormal cells that have changed, or mutated, from normal cells, it is also known as neoplasm or tumor It is a group of cells, usually derived from a single cell, that has lost its normal control mechanisms and thus has unregulated growth. Cancerous (malignant) cells can develop from any tissue within any organ. As cancerous cells grow and multiply, they form a mass of cancerous tissue, called a tumor, which invades and destroys adjacent healthy tissue. Tumors generally provide no useful function and grow at the expense of healthy tissues. This growth prevents normal function of vital organs and can cause organ failure. Cancerous cells from the primary (initial) site can spread (metastasize) throughout the body. The growth of tumour persists in the same excess even after cessation of the stimuli/etiology. Oncology is branch of science which deals with the study of tumours (Oncos=tumour, logos=study) (Ezra, 2002; Stephen, 2004; Merck Source.htm).

Neoplasm is a general term for a tumor, whether cancerous or non-cancerous. The word neoplasm has been derived from Greek language means "New formations or new growth" (Neo=new, plasm=growth). It can be defined as "*A mass of tissue formed as a result of abnormal, excessive, uncoordinated, autonomous and purpose less proliferation of cells*" and is characterized by key features of continuous growth, resemblance to embryonic cells, no structural/orderly arrangement, no useful function and no clear etiology. A neoplastic growth does not obey the laws of the healing or normal tissue growth, and its cells continue to multiply indefinitely irrespective of any structural or functional requirements and form an ever increasing mass of tissue.

CLASSIFICATION

Tumors are classified as either benign or malignant.

Benign: These are slow-growing and often harmless depending on the location. It is non-cancerous in nature. In Benign tumours, the cells are of adult type. These neoplams are well differentiated, grow slowly by expansion and do not invade below basement membrane. They remain localized, encapsulated and can be removed by surgery. They are classified with addition of a suffix-oma to the cell type. e.g. Fibroma, Chondroma, Adenoma, Papilloma.

Malignant: Malignant tumors are what we call cancer. These are faster-growing and likely to spread to other parts of the body and cause severe problems. The invasive capacity of a cancer to infiltrate and destroy surrounding tissue affects its spread. Cancerous cells spread to a completely new location by metaplasia. In malignant tumors the cells are having characteristics of embryonic stages. This reversion towards cells to a more primitive or embryonic and less differentiated type is also known as anaplasia. The more anaplastic cells we see in a tumour more malignancy will be there. It will depend on the degree of anaplasia in which malignant cells characteristically show enlargement of nucleus, multiple nuclei, (tumour giant cells), enlargement of nucleolus, increase number of mitotic figures, hyperchromasia and embryonic type features. Thus, the neoplastic cells are anaplastic, metastasize and invade the adjacent tissues and destroy normal tissue. They are also called as cancer meaning "like crab". They can adhere to any part of body. They are classified with suffix as carcinoma or sarcoma. Ectodermal origin- Carcinoma, Mesodermal origin- Sarcoma. e.g. Lymphosarcoma, Adenocarcinoma, Squamous cell carcinoma. Some tumors are highly undifferentiated they are referred as "undifferentiated malignant tumours".

NEOPLASTIC CELL STRUCTURE

Anaplasia: More anaplasia represents more undifferentiated neoplasm.

Loss of contact: Neoplastic cells loss contact with neighbouring cells due to decreased adhesiveness. It helps in invasion and metastasis.

Neoplastic cell lack contact inhibition: It helps in the growth/spread of tumours.

Abnormal cytoskeleton of cells: Its unstable chromosome movements cause abnormality in cytoskeleton.

Chromosomal defects: Malignant cells are usually aneuploid i.e. cells having more or less than diploid number of chromosomes. This gives a pathologic karyotype in the form of chromosomal breaks or translocations. e.g.. Plasmacytoma (tumour of B-lymphocytes) in which translocation of segments of chromosome 15 occurs to chromosome 12.

ETIOLOGY AND RISK FACTORS

In general, tumors appear to be caused by abnormal regulation of cell division. Typically, the division of cells in the body is strictly controlled and regulated. New cells are created to replace older ones or to perform new functions. Cells that are damaged or

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no longer needed die to make room for healthy replacements. If the balance of cell division and death is disturbed, a tumor may form. Carcinogen is an agent that causes cancer and includes many chemicals (arsenic, asbestos, aromatic amines, benzene, chromates, nickel, vinyl chloride, mineral oil, diesel exhaust), medicinal/therapeutic agents (alkylating agents, chemotherapy drugs such as topoisomerase inhibitors, diethylstilbestrol, radiation therapy), betel nuts, tobacco, certain viruses, poisonous mushrooms, aflatoxins etc. The time between exposure to the chemicals and development of the cancer may be many years. Other factors include genetic abnormalities, radiation, excessive sunlight exposure, alcoholism, obesity and sedentary lifestyle. Tobacco causes more deaths from cancer than any other environmental agent. Abnormalities of the immune system, which usually detects and blocks aberrant growth, can also lead to tumors.

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Instrinsic or Predisposing Factors

Family History and Genetic/Heredity factors: History of genetic abnormalities and an extra or abnormal chromosome may increase the risk of cancer. Some chicken are susceptible for leucosis while others are resistant for leucosis. Pigmentation also effects the cancer development. In white horses Melanosarcoma is common. Squamous cell carcinoma is common in hereford cattle.

Sex and Age: Some tumors are more common in one sex than the other, some are more common among children or the elderly. However, most cancers are more common in older people. The increased cancer rate is probably due to a combination of increased and prolonged exposure to carcinogens and weakening of the body's immune system. Tumors of genital tract are common in females.

Extrinsic Factors

Physical factors: Extended exposure to ultraviolet radiation (UV-rays), X-rays, radium, ionizing radiation primarily from sunlight, causes skin cancer. Ionizing radiation is particularly carcinogenic.

Chemical factors: Many chemicals are known to cause cancer and many others are suspected of doing so. *Initiators:* Coal-tar, Aflatoxins, Actinomycin D, Mitomycin, Alkylating agents (Cyclophosphamide, Nitrosourea), Polycyclic aromatic hydrocarbons (Tobacco, Smoke, Pollutants), Benzanthracene, Arsenic, Metals (Nickel, Lead, Cobalt, Chromium), Insecticides (Aldrin, Dieldrin, Chlordane). *Promoters:* Phenols, Hormones (Estrogen), Drugs (Phenobarbital), Artificial sweetners (saccharine, colouring/flavouring agents and preservatives.

Environmental Factors: Pollution in the air, whether from industrial wastes or cigarette smoke, can increase the cancer risk. For example, asbestos exposure may cause lung cancer. Smoking cigarettes produces carcinogens that substantially increase the risk of developing cancers of the lung, mouth, larynx, kidney, and bladder.

Viral Infections: Several viruses are known to cause cancer in humans, and several others are suspected of causing cancer. The papillomavirus (which causes genital warts) is one cause of cervical cancer in women. Hepatitis B virus can cause liver cancer. Some human retroviruses cause lymphomas and other cancers of the blood system. Epstein-Barr virus causes Burkitt's lymphoma. Other viruses causing cancers include Polyoma virus, Adeno virus, Poxvirus, Hepdna virus (Hepatitis B virus – hepatocellular carcinoma), Retrovirus and Herpes virus.

Other factors

Geography: The geographic variation in cancer risk is probably multifactorial: a combination of genetics, diet and environment.

Diet: A diet high in fat has been linked to an increased risk of colon, breast, and possibly prostate cancer. People who drink large amounts of alcohol are at much higher risk of developing esophageal cancer. A diet high in smoked and pickled foods or in barbecued meats increases the risk of developing stomach cancer.

Inflammatory Diseases: Ulcerative colitis can result in colon cancer. Infection with the parasite *Schistosoma (Bilharzia)* may cause bladder cancer by chronically irritating the bladder.

DEVELOPMENT AND SPREAD

Cancer occurs when cell division gets out of control. Usually, the timing of cell division is under strict constraint, involving a network of signals that work together to say when a cell can divide, how often it should happen and how errors can be fixed. Mutations in one or more of the nodes in this network can trigger cancer, be it through exposure to some environmental factor (e.g. tobacco smoke) or because of a genetic predisposition, or both. Usually, several cancer-promoting factors have to add up before a person will develop a malignant growth. The predominant mechanisms for the cancers development are (i) impairment of a DNA repair pathway (ii) the transformation of a normal gene into an oncogene and (iii) the malfunction of a tumor supressor gene.

Neoplastic cell genesis (Carcinogenesis)

Cell differentiation: Specialized cells derived from less specialized cells (embryonic cells) are controlled by specific gene. Cells become differentiated so that the genes that control embryonic characters are switched off and genes for more differentiated characters are activated. In neoplastic cells, the presence of abnormal genes (genetic mechanisms) or normal genes expressed at abnormal level (epigenetic mechanism) favour proliferation over differentiation.

Genetic mechanisms: Mutation in a somatic cell nucleic acid occurs to provide a stable and monoclonal population of cells.

Epigenetic mechanism: Genome is normal in cancer cell but transcription and translation is abnormal which is responsible for abnormal growth of cells.

In most tumors genetic mutation or genetic rearrangement occurs like DNA transcribe to mRNA and mRNA translated to protein (enzymes) which direct cells for proliferation. Changes occur in DNA as a result of direct chemical or radiation damage or there is insertion of viral genes to host DNA that induces cell proliferation through neutralizing normal growth controlling gene. Tumors do not arise from completely differentiated cells such as neurons or keratinized epithelial cells, but stem cells (pluripotential) must be present for the growth of tumour. Neoplastic cells do not "dedifferentiate" but fail to respond to normal signals for differentiation. Cancerous cells develop from healthy cells in a complex process called transformation. The first step in the process is initiation, in which a change in the cell's genetic material, in the DNA and sometimes in the chromosome structure, primes the cell to become cancerous. This change in the cell's genetic material may occur spontaneously or be brought on by an agent that causes cancer (a carcinogen). However, not all cells are equally susceptible to carcinogens. A genetic flaw in a cell may make it more susceptible. Even chronic physical irritation may make a cell more susceptible to carcinogens. The second step in the development of cancer is called promotion. Agents that cause promotion are called promoters, which may be substances in the environment or even some drugs (such as barbiturates). Unlike carcinogens, promoters do not cause cancer by themselves. Instead, promoters allow a cell that has undergone initiation to become cancerous. Promotion has no effect on non-initiated cells. Thus, several factors, often the combination of a susceptible cell and a carcinogen, are needed to cause cancer. Some carcinogens are sufficiently powerful to be able to cause cancer without the need for promotion. For example, ionizing radiation, used in X-rays and produced in nuclear power plants and atomic bomb explosions can cause a variety of cancers, particularly sarcomas, leukemia, thyroid cancer and breast cancer.

Viral Oncogenesis: Oncogenes are the transforming genes present in most tumor cells of animal and man. It is also present in certain viruses. Experimentally, when they are incorporated in cells in culture, the cells get transformed to multiply. When such genes are present in normal cells that are known as cellular oncogenes (c-oncs) or proto-oncogenes, which are present in a wide range of cells and has a physiological role of proliferation of cells through protein product. Proto-oncogenes are converted into active oncogenes through mechanisms of point mutation, translocation, gene amplification, inappropriate expression of proto-oncogenes and integration of viral DNA into host cell DNA. The integration of viral DNA into host cell DNA causes adjacent gene activated for growth of the cell without control. Some of the viral oncogenes (v-oncs) are: *src* (Rous sarcoma Virus), *myc*, *myb, erb-B, erb-A* (Avian leucosis virus), *pim-1*, *myc* (Feline leukemia Virus), *src, raf, myc* (Papilloma virus), *hap* (Hepadna virus), *rel (*Reticuloendotheliosis), *yes, ros* (Avian sarcoma virus) and *fes, fms* (Feline sarcoma virus).

Antioncogenes are genes that suppresses the cellular proliferation. So neoplastic growth occurs either as a result of activation of oncogene or due to inactivation of antioncogene.

Telomeres: These are unique DNA-protein structures that contain noncoding TTAGGG repeats and telomere-associated proteins, which are essential for maintaining genomic integrity. Alterations that lead to the disruption of telomere maintenance result in chromosome end-to-end fusions and/or ends being recognized as double-stranded breaks. It is suggested that cell responds to dysfunctional telomeres by undergoing senescence, apoptosis, or genomic instability. In conjunction with other predisposing mechanisms, the genomic instability encountered in preimmortal cells due to dysfunctional or uncapped telomeres might lead to cancer. Genomic instability is one of the earliest neoplastic changes known to occur in most cancers and leads to mis-regulation of genes involved in growth control, ultimately resulting in tumorigenesis. Telomere dysfunction has been proposed to play critical roles in aging as well as cancer progression. The greatest risk factor for cancer in humans is growing older. Genetic alterations must occur within multiple growth control pathways before normal cells are converted into cancer cells. Inducing short telomeres or loss of capping can sensitize cells to death via DNA damaging reagents or ionizing radiation.

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Neoplastic Cell Metabolism

Normal regulation of programmed protein synthesis is lost in neoplastic cells. Gene expression and mRNA translation is being directed towards purine synthesis to meet the requirements of mitosis; defective sodium pump (ATPase) due to abnormal receptor molecules and glycoproteins on neoplastic cells; and increased glycolysis due to damage in self replicating DNA of moitochondria, overproduction of inorganic phosphorous due to high rate of ATP hydrolysis and abnormal enzymes on cell surface.

Spread of Neoplasms

Expansion: Benign tumors are encapsulated and surrounded by fibrous tissue and hence they do not infiltrate in neighbouring tissue. However, they expand as their growth increases.

Distant spread/metastasis: Metastasis is the movement or spreading of cancer cells from one organ or tissue to another. Cancer cells usually spread via the bloodstream or the lymph system. It is the spread of tumors by invasion in such a way that detached tumor mass may form secondary tumor at the site of lodgment. They can grow directly into surrounding tissue or spread to tissues or organs, nearby or distant. Cancer spreads throughout the body shortly after the tumor cells develop the ability to invade blood and lymph vessels. Such spread may be overt, in the form of visible metastases, or undetectable, in the form of micrometastasis. Carcinomas typically spread through the lymphatic system. For example, breast cancer usually spreads first to the nearby lymph nodes and then it spreads more extensively throughout the body. Sarcomas spread via the bloodstream. Most of the malignant tumors metastasize except malignant tumor of central nervous system and basal cell carcinoma of skin. The process of metastasis includes 5 steps viz. penetration (invasion), separation, dissemination, establishment and subsequent proliferation.

There are several methods of metastasis, which are as under:

Infiltration: Neoplastic cells infiltrate or invade the surrounding tissue. Various factors responsible for invasion are growth of new cells, lack of contact inhibition, motility of malignant cells, secretion of lytic enzymes, role of chemotactic factors and activation of complement.

Lymphatic spread: Epithelial tumors like carcinomas spread through lymphatic route. Cancer cells invade the wall of lymphatics which is known as lymphatic permeation and form tumor emboli. These cells are lodged in subcapsular sinus of lymph node and may grow. Nearest lymph node initially act as barrier filter and kill the tumor cells but later it provides fertile environment for growth of tumor cells. Obstruction of lymphatics by tumor cells also disturbs the lymphatic flow and is responsible for metastasis at unusual sites.

Hematogenous spread: Metastasis through blood is common route for most of the sarcomas (connective tissue tumors). Some carcinomas (lung, mammary gland, thyroid, kidney) may spread through blood. Common sites of lodgment of tumor cells are liver, lungs, kidneys, brain and bones. Cancer cell invade the wall of capillaries to form tumor emboli. Blood borne metastasis appear as multiple and rounded nodules scattered in the organ.

Transcoelomic spread: The tumor cells invade serosal wall and enters in coelomic cavity and then tumor cells implant at another place, e.g. Peritoneal cavity- carcinoma of stomach/ovary.

Spread along epithelial lined surfaces: The neoplasms of epithelium spread along the line of basement membrane without damaging it, e.g. spread of tumor through fallopian tube from ovaries to endometrium, and spread of tumor through bronchus to alveoli.

Spread via cerebrospinal fluid (CSF): Tumor of meninges may spread through cerebrospinal fluid as the detached tumor cells metastasize at other sites in central nervous system through CSF.

Implantation: It is a very rare method of spread of tumors. In this the tumor cells are implanted at another site inadvertently, e.g. Surgeon's scalpel, needle, sutures may transfer tumor cells from one to another place in body; Cancer of lower lip may metastasize to upper lip.

Cancer is more likely to progress in people whose immune system is altered or impaired, as in people with acquired immunodeficiency syndrome (AIDS), those receiving immunosuppressive drugs, those with certain autoimmune diseases, and older people, in whom the immune system works less well than in younger people. However, even when a person's immune system is functioning normally, cancer can escape the immune system's protective surveillance.

SYMPTOMS AND SIGNS

Cancer can produce many different symptoms but some tumors produce no symptom. Symptoms depend on the type and location of the tumor. Some symptoms occur with many or almost all cancers, and others are specific to the type of cancer and where it is growing. For example, lung tumors can cause coughing, shortness of breath, or chest pain while tumors of the colon can cause weight loss, diarrhea, constipation and

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blood in the stool. At first, cancer, as a tiny mass of cells, produces no symptoms whatsoever. When cancer grows in an area with a lot of space, such as in the wall of the large intestine, it may not cause any symptoms until it becomes quite large. In contrast, a cancer growing in a more restricted space, such as on a vocal cord, may cause symptoms (such as hoarseness) when it is relatively small. Cancers produce symptoms by growing into and thus irritating or destroying other tissues, putting pressure on other tissues, producing toxic substances, and using energy and nutrients normally available for other bodily functions. It may cause one set of symptoms as it grows in its initial site and cause different symptoms as it spreads (metastasizes) to other parts of the body. Some symptoms develop early in the course of cancer and are therefore important warning signs that should be evaluated by a doctor. Other symptoms develop only after the cancer progresses and are therefore not helpful in the early detection of cancer. General symptoms that often accompany tumors (warning signs of cancer) include: fevers, recurrent fever, chills, night sweating, persistent pain, recurrent nausea, weight loss, loss of appetite, sudden depression, fatigue, malaise, vomiting, a recent change in bowel habits (constipation or diarrhea), blood in urine/stool (either visible or detectable by special tests), chronic cough, changes in the size or color of a mole or changes in a skin ulcer that does not heal, enlarged lymph nodes etc.

Cancers are typically painless at first. However, as they grow, the first symptom is often a mild discomfort, which may steadily worsen into increasingly severe pain as the cancer enlarges. The pain may result from the cancer compressing or eroding into nerves or other structures. This may cause several neurological and muscular symptoms, including a change in sensations (such as tingling sensations) or muscle weakness. As the cancer enlarges and invades surrounding tissues, it may grow into a nearby blood vessel, causing bleeding. The bleeding may be slight and undetectable or detectable only with testing. Particularly with advanced cancer, the bleeding may be massive and even life threatening. As a cancer begins to spread, it may first spread to nearby lymph nodes, which become swollen and may be felt as hard or rubbery. Cancer can compress or block structures, such as the airways in the lungs, causing shortness of breath or pneumonia and the inability to cough up secretions. When a cancer grows in the brain, symptoms may be hard to pinpoint but can include confusion, dizziness, headaches, nausea, changes in vision, and seizures. People with advanced stage cancer are often may find that they feel very tired or become short of breath when exerting themselves, fatigued and loose weight. They sleep many hours a day. Depression can be related to the symptoms of the illness, a fear of dying, and a loss of independence. Cancer produces both direct and indirect effects on bone health. Bone metastases cause considerable morbidity, including severe pain, impaired mobility, symptoms of hypercalcemia, pathologic fractures due to reduced load-bearing capabilities, and spinal cord compression. Cord compression can lead to paralysis or death. Hypercalcemia is potentially lethal and may cause dysfunction of the gastrointestinal tract, kidneys, and central nervous system. Pain is often the first indication that the tumor has metastasized to the bone, which in turn has a detrimental affect on a patient's quality of life, interfering with daily activities and limiting a patient's capabilities. These effects often lead to feelings of anger, fear, and depression.

The size of a tumour varies from one mm to several centimeter diameter. The common warts/ papilloma over skin have smaller size while certain tumors have many centimeter diameter such as uterine tumors etc. The weight of tumor also varies from few milligram to several kg. The consistency of a tumour depends on the type of tissue involved. The tumour of bone is hard while connective tissue tumors are firm and dense or sclerotic. Brain tumors are mostly soft. Microscopically, the tumour is composed of cells, which resembles the type of tissue/organ involved. The appearance of cells vary on degree of malignancy.

CLINICOPATHOLOGICAL EFFECTS OF NEOPLASMS

Malignant neoplastic cells kill humans and animals through many effects which are categorized into local and systemic effects.

Local effects: The main local effect is pressure on surrounding tissue. The tumor causes pain, ischemia, oedema and lymphatic blockade in surrounding tissue. The lumen of ducts are obstructed due to pressure from outside tumors. e.g. squamous cell carcinoma of respiratory tract causes dyspnoea and hypoxia due to obstruction in pharynx. Tumors which cause obstruction in urinary tract or obstruction in bile ducts may lead to death.

Systemic effects

Cachexia: Cachexia is main characteristic feature of malignant tumors. In later stages, anorexia occurs in leading to loss of weight and letharginess. Anorexia occurs due to depression of appetite centre in brain. A humoral factor is released by tumour cells that causes suppression of appetite centre in brain. Cytokines secreted by tumor cells or by altered macrophages

(affected by neoplastic cell) are known as cachectin which causes suppression of gene that produces lipogenic enzymes responsible for fat deposition. Neoplastic cells act as amino acid trap and thus, drain out the essential amino acids leading to regression of skeletal muscles, liver, pancreas and other organs. Hepatocytes become atrophied.

Hypoglycemia: It is characteristic feature of tumors of pancreas and other epithelial tumors. It is characterized by restlessness, weakness, tremors, episodes of collapse and seizures.

Anemia: Anemia is a common feature in all metastatic tumors. It is caused by haemorrhage through invasion by cancer cells, decreased erythropoiesis due to invasion of tumour cells in bone marrow, increased erythrocyte fragmentation as many blood vessels pass though tumors. In highly vascular tumor, there are more chances of anemia. In hyperspleenism, there is spleenomegaly due to excessive removal of RBC from circulation. Iron deficiency due to tumor may also lead to anemia. Due to anticancer therapy there is non regeneration of stem cells. It causes death of stem cells or dividing cells of bone marrow leading to anemia. Autoimmune anemia occurs in lymphoid neoplasms and there is suppression of erythropoitin by kidneys.

Thrombocytopenia: In tumor patients thrombocyte production is reduced. e.g. in viral leukemia, platelet survival rate is reduced from 40-80% in dogs.

Thrombosis: Tumor cells produce procoagulants which are responsible for intra vascular coagulation and thrombi formation.

***Hypercalcemia*:** In most of the malignant neoplasms, hypercalcemia occurs through two mechanism. In solid tumors due to osteolytic metastasis excessive bone resorption occurs leading to calcium release. Tumour cell also secrete proteins that increases parathyroid hormone leading to increase in calcium level in blood. Pseudohyperpara-thyroidism is associated with mammary gland cancer, fibrosarcoma, lymphosarcoma and adenocarcinoma in dogs and gastric carcinoma in horses.

Diarrhoea: Prolonged diarrhoea occurs in malignant neoplasms which is unresponsive to therapy and non associated with microorganisms. Neoplastic cell secretes vasoactive intestinal peptides that cause diarrhoea leading to death of the affected individual.

Fever: Some tumor cells release pyrogens that increases body temperature which is anti neoplastic in nature. In late stage of metastatic tumors fever is a characteristic feature.

TUMOR COMPLICATIONS

Complications can occur if a tumor is located in a region of the body where it compromises the function of the normal organ. When a malignant tumor grows and spreads throughout the body, a number of complications can result, depending on the degree to which a tumor grows and spreads i.e. its aggressiveness. The diagnosis of cancer often causes a lot of anxiety and can affect one's entire life. Some of these complications can be serious and require emergency treatment. Paraneoplastic syndromes occur when a cancer produces one or more substances that circulate in the bloodstream, such as hormones, cytokines (a type of protein), or other proteins and thus spread throughout the body. These substances can affect the function of other tissues and organs. Some substances damage organs or tissues by causing an autoimmune reaction. Others directly interfere with the function of different organs or actually destroy tissues. Symptoms such as low blood sugar, diarrhea, and high blood pressure can result. Cardiac temponade occurs when fluid accumulates in the baglike structure surrounding the heart (pericardium, or pericardial sac), when a cancer invades the pericardium and irritates it and which puts pressure on the heart and interferes with its ability to pump blood. This can be observed with lung cancer, breast cancer, and lymphoma. Pleural effusion occurs when fluid accumulates in the pleural sac of lungs, causing shortness of breath. Superior vena cava syndrome occurs when cancer partially or completely blocks the superior vena cava causing the veins in the upper part of the chest and neck to swell, resulting in swelling of the face, neck, and upper part of the chest. Spinal cord compression occurs when cancer compresses the spinal cord or the spinal cord nerves, resulting in pain and loss of function.

Brain dysfunction occurs when the brain functions abnormally as a result of a cancer growing within it, either as a brain cancer or more commonly as a metastasis from a cancer elsewhere in the body. Many different symptoms can occur, including confusion, sedation, agitation, headaches, abnormal vision, abnormal sensations, weakness, nausea, vomiting, and seizures. Polyneuropathy occurs as a dysfunction of peripheral nerves, resulting in weakness, loss of sensation, reduced reflexes and incoordination. Subacute cerebellar degeneration occurs in women with breast or ovarian cancer, due to an autoantibody that destroys the cerebellum. Symptoms are unsteadiness in walking, incoordination of the arms and legs, difficulty in speaking, dizziness, and double vision, which may

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appear weeks, months, or even years before the cancer is detected and often result in severe disability. Spasms of the eye and muscles and lack of coordination of movements can occur in some children with neuroblastoma. Hypertrophic osteoarthropathy can also occur in people with lung cancer, in which the shape of the fingers and toes and causes changes at the ends of long bones. Squamous cell carcinoma may secrete a hormone like substance that leads to very high calcium levels in the blood (hypercalcemic syndrome). This may also be the result if the cancer directly invades bone, thereby releasing calcium into the bloodstream, which can progress to coma and even death. Other problems include breast enlargement in men (gynecomastia), an excess of thyroid hormone (hyperthyroidism), and skin changes, including darkening of the skin in the armpits. People with cancer are at risk for developing nutritional deficiencies. The deficiencies may be the result of the cancer itself, or the side effects of common cancer treatments such as surgery, chemotherapy, and radiation therapy. Malignancies directly compromise nutritional status by altering metabolism and causing loss of appetite. There are also individual alterations in carbohydrate, protein, and fat metabolism. These changes contribute to the loss of skeletal muscle and adipose tissue (fat) stores. Cancer-associated anorexia is probably the result of physiological changes but may also be due to a psychological response to the disease. Malignancy can adversely affect food and nutrient ingestion, tolerance, and utilization.

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DIAGNOSIS

Diagnosis of cancer/neoplasms can be done on the basis of symptoms and lesions, clinicopathological effects, immunological methods by using tumor markers and gross and microscopic features (histopathological examination) and employing recent diagnostic tools and technologies. The symptoms and signs of tumors vary based on their site and type. Some symptoms may give early warning of cancer and should, therefore, trigger a person to seek medical care. Fortunately, most of the symptoms are usually caused by far less serious conditions. Nonetheless, the development of any of the warning signs of cancer should not be ignored. Diagnosis encompasses screening, testing, and a physical examination. For diagnosing and staging cancers and to determine whether the cancer has spread in the body the tests include: Computed tomography (CT) scan, magnetic resonance imaging (MRI), positron emission tomography (PET) scan, complete blood count (CBC), blood chemistries, biopsy of the tumor, bone marrow biopsy (most often for lymphoma or leukemia), endoscopy usually guided by a CT scan, barium X-ray, chest X-ray, mammogram, bone scans, ultrasound, blood tests for liver enzymes, sputum cytology, radioisotope scan, exploratory surgery, barium enema examination and testing for tumor markers/antigens. These tests vary with the location of the tumor in the body. When a tumor is found, a biopsy is performed to determine if the tumor is benign or malignant, which is important in both diagnosis and staging. Depending on the location of the tumor, the biopsy may be a simple procedure or a serious operation. Biopsies are often needed to be sure that an abnormality discovered on an imaging test is cancer. Many kinds of biopsies can be performed with a needle and do not require surgery. Sometimes, however, surgery is needed to obtain a sample of tissue. Physical examination and whole-body photography is done for skin cancer, stool examination for occult blood, rectal examination for rectal and colon cancer, pelvic examination and Pa panicolaou (Pap) test for cervical cancer, physical examination and mammography for breast cancer. Most patients with tumors undergo CT scans or MRI to determine the exact location of the tumor and its extent. In MRI, a very powerful magnetic field generates and exquisitely detailed anatomic images are obtained. MRI is of particular value in detecting cancers of the brain, bone and spinal cord. More recently, PET scans have been used to visualize tumors, by measuring biochemical processes within it. Monoclonal (one-cell type) antibodies, which can selectively bind to unique tumor antigens can be used diagnostically when linked with low-intensity radionuclides. The patient is then “scanned” with a gamma counter, and any areas of localized radiation emission (possible cancer lesions) can be identified.

Screening programs allow early detection and diagnosis of cancer and serve to detect the possibility that a cancer is present before symptoms occur. Screening for cancers can help prevent tumors or detect them at their earliest and most treatable stages. Because cancer is more likely to be cured if treated early, it is critical that cancer be discovered early. These usually are not definitive; results are confirmed or disproved with further examinations and tests. Although screening tests can help save lives, they can be costly and sometimes have psychologic or physical repercussions. In women, two of the most widely used screening tests are the Papanicolaou (Pap) test to detect cervical cancer and mammography to detect breast cancer. In men, a common screening test involves measuring the level of prostate-specific antigen (PSA) in the blood. PSA levels are high in men with prostate cancer, but levels

are also elevated in men with noncancerous (benign) enlargement of the prostate. Finding occult blood in the stool in older people is an indication that something is wrong in the colon. The problem may be cancer, although many other disorders can also cause small amounts of blood to leak into the stool. Some screening tests can be done at home. For example, monthly breast self-examinations are valuable in helping women detect breast cancer. Periodically examining the testes can help men detect testicular cancer, one of the most curable forms of cancer, especially when diagnosed early. Periodically checking the mouth for sores can help detect mouth cancer in an early stage.

When cancer is diagnosed, staging tests help determine how advanced the cancer is in terms of its location, size, growth into nearby structures, and spread to other parts of the body. Staging allows doctors to determine the most appropriate treatment as well as helping to determine prognosis.

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Tumor Markers/Antigens*:*

Tumor markers are substances secreted into the bloodstream by certain tumors and can be detected with blood tests. These are fetal antigens and alpha fetoproteins produced by embryonic cells. It is produced by liver cells but after birth it's production is stopped normally. It is a differentiation antigen as in normal cells or viral antigens on cell surface., e.g.. Retrovirus. Tumor antigens have been identified in several types of cancer, including malignant melanoma, bone cancer (osteosarcoma), and some cancers of the digestive tract. Sometimes these are used for diagnosis and sometimes to evaluate the person's response to treatment. Measurements of some of the tumor markers can be used as screening tests in people who have no symptoms of cancer. However, tumor markers sometimes are present in the blood of people who do not have cancer. Thus, finding a tumor marker does not necessarily mean a person has cancer. But, in people who do have cancer, tumor markers can be used to monitor the effectiveness of treatment and to detect possible recurrence of the cancer. If the tumor marker was present before treatment but no longer appears in a blood sample after treatment, the treatment has probably been successful. If the tumor marker disappears after treatment then later reappears, the cancer has probably returned i.e. the level of a tumor marker increases if the cancer recurs.

Carcinoembryonic antigen (CEA): Levels are raised in the blood of people with cancer of the colon, breast, pancreas, bladder, ovary, or cervix. Levels may also be raised in people who are heavy cigarette smokers and in those who have cirrhosis of the liver or ulcerative colitis.

Alpha-fetoprotein (AFP): Normally produced by fetal liver cells, AFP is found in the blood of people with liver cancer (hepatoma). AFP is often also found in people with certain cancers of the ovary or testis and in children and young adults with pineal gland tumors.

Beta-human chorionic gonadotropin (ß-HCG): This hormone is produced during pregnancy but also occurs in women who have a cancer originating in the placenta and in men with various types of testicular cancer.

Prostate-specific antigen (PSA): Levels are raised in men with noncancerous (benign) enlargement of the prostate and are considerably higher in men with prostate cancer.

Carbohydrate antigen 125 (CA-125): Levels are raised in women with a variety of ovarian diseases, including cancer.

Carbohydrate antigen 15-3 (CA 15-3): Levels are raised in people with breast cancer.

Carbohydrate antigen 19-9 (CA 19-9): Levels are raised in people with cancers of the digestive tract, particularly pancreatic cancer.

Beta$_2$ (ß$_2$)-microglobulin: Levels are raised in people with multiple myeloma, chronic lymphocytic leukemia, and in many forms of lymphoma.

Lactate dehydrogenase: Levels can be raised for a variety of reasons, and particularly in people with testicular cancer, melanomas, and lymphomas.

IMMUNE MECHANISMS:

In some individuals the growth of neoplasm is very fast that leads to early death. In others, tumor growth is slow and the individual may survive several years. When malignant tumor is clinically manifested it takes 6 month to 1 year to cause death. There are many systems/ functions in the body which works together to fight with neoplastic cells.

Nonspecific lysis and phagocytosis: Most tumor cells are phagocytosed by polymorphonuclear cells and macrophages. On contact, macrophages insert cytoplasmic processes into the tumor cells and transfer lysosomal enzymes into the cytoplasm of cancer cell leading to death of cell. Because in cancer cell decreased catalase and glutathione contents makes them susceptible to oxidative injury by macrophages. On the contrary reactive oxygen metabolites of neutrophils "respiratory burst" are mutagenic and may act as tumor promoter.

Natural killer cell: It is a population of immature lymphocytes which bears Fc receptor that causes lysis of neoplastic cells or virus infected cells.

Antibodies: Antibodies against tumor antigens also restrain the growth of tumor.

Tumour antigens: Tumour cells develop certain biochemical alterations on their surface (protein change) that makes the "tumour" antigens". These are useful in differentiating between neoplastic or preneoplastic cell. These antigens may evoke immune response in body by humoral or cell mediated mechanism which may inhibit the tumour cell growth. Tumour antigens induced selective CMI response which destroys the malignant cells. During cytological or histological examination of biopsy material, if one finds lymphocytes along with cancer cells, the prognosis is considered as good. *Propionibacterium acnes (Corynebacterium parvum),* BCG and filterate of G-ve bacterial cultures are used to stimulate the reticulo-endothelial system against tumors. Macrophages attract and attach on tumor growth and remove it through phagocytosis. e.g. in ocular squamous cell carcinoma, intra tumor injection of BCG reduces growth by 71%. In early tumor growth, tumor cells excrete some products that inhibits the macrophages, e.g. macrophages also release certain soluble factors that are having anti-tumour activities, such as tumour necrosis factor (TNF) which causes necrosis of tumor cells. It needs to be activated by *P. acnes* or LPS of G-ve bacteria. It affects subcutaneous transplantation of tumor.

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Escape of neoplastic cells from immunological destruction

Delayed immunostimulation: The tumor antigens appear late on the anaplastic/neoplastic cell surface causing delayed immune response.

Antigenic modulation: Frequent change in antigenic determinants over neoplastic cell surface may escape the cell from immune response.

Antigenic overload: There are too many antigenic determinants on the neoplastic cell surface that leads to immune tolerance.

General immunodeficiency Neoplasia, in general, causes immunosuppression in body.

Specific immunodeficiency: There is lack of recognition of tumor antigens on neoplastic cells by the immunocytes that leads to suppression of specific immune response.

Humoral antibodies: Antibodies binds with tumor antigens and blocks the effect of more potent anti-neoplastic action by another source.

TREATMENT:

Treating cancer is one of the most complex aspects of medical care. Successful treatment of cancer requires elimination of all cancer cells, whether at the primary site, extended to local-regional areas, or metastatic to other regions of the body, and with the result that the specific cancer will not grow back. Treatment also varies based on the type of tumor, whether it is benign or malignant, and its location. If the tumor is benign and is located in a "safe" area where it will not cause symptoms or disturb the proper functioning of the organ, sometimes no treatment is needed. Sometimes benign tumors may be removed for cosmetic reasons. A variety of approaches are used to treat cancer that has spread beyond the regional place like application of surgery, radiation, chemotherapy, hormone therapy, and immunotherapy using biologic response modifiers. If all of the cancer cannot be removed with surgery, the options for treatment include radiation and chemotherapy, or both. Some patients require a combination of surgery, radiation and chemotherapy.

Cancer therapy involves a team that encompasses many types of doctors working together (for example, primary care doctors, gynecologists, oncologists, surgeons, radiotherapists, and pathologists) and many other types of health care workers (for example, nurses, physiotherapists, social workers, and pharmacists). Treatment decisions take into account many factors, including the likelihood of cure or of prolonging life when cure is not possible, the effect of treatment on symptoms, the side effects of treatment, and reduce the chance of spread (metastases). People undergoing cancer treatment hope for the best outcome and the longest survival with the highest quality of life. Even when a cure is impossible, symptoms resulting from the cancer can often be relieved with treatment that improves the quality and length of life (palliative therapy). However, people who are candidates for radiation therapy or anti-cancer drugs must understand the risks involved with treatment. Therefore it should be ensured that people receive the most effective care with the fewest side effects (Groenwald *et al.*, 1997).

Surgery: Historically, until the advent of radiotherapy and chemotherapy, surgery was the only available technique for treating cancer. It still is the primary method for curing about one-third of cancer patients with localized tumors i.e. the cancer confined to one location. Cancer is most curable surgically when the lesion is small and has not metastasized. If the lesion and a small margin of surrounding healthy tissue are removed, the chance of curing most tumor types, if no metastases are present, is good. If it has spread to local lymph nodes only, sometimes can also be removed. Patients with distant metastases are not curable

surgically, although palliative resection is sometimes indicated. Premalignant, also called precancerous, lesions can also be cured by surgical removal. These tend to progress to malignant lesions, if not properly treated. Surgery may be performed for palliative reasons to reduce the tumor burden and/or to relieve symptoms. Decreasing the tumor mass (debulking) may increase the response to chemotherapy and/or radiotherapy in some tumors, such as ovarian cancer. Surgery is also used for diagnosis and/or staging, as in Hodgkin's disease and ovarian cancer, wherein the extent of treatment is dictated by the stage of disease. Surgery is used in the cancers such as all cancers of the gastrointestinal tract and accessory structures, gallbladder, bone, breast, endometrium (the lining of the uterus), eye, genitalia, cervix, ovary, larynx, lung, melanomas, many head and neck cancers, most skin cancers, renal (kidney) cancer, salivary gland, sarcomas (cancer of the connective tissue), some brain tumors and thyroid tumors. Surgery is never curative in disseminated cancer (Sabiston, 1991).

Radiotherapy: It is a treatment approach that uses radiation (x-rays or related radiation) to destroy cancer cells. Radiation preferentially kills cells that divide rapidly. Cancer cells usually multiply faster than other cells in the body and therefore are more likely than most normal cells to be killed by radiation. Radiation prevents the cancerous cells from continuing to reproduce and thus prevents the tumor from growing further. Cancer cells differ in how easily they are killed by radiation, some are very resistant and thus cannot be effectively treated. Radiation therapy is thought to stop the growth of malignant lesions by damaging the DNA within the cancer cells. It involves a field of intense energy focused on a certain area or organ of the body. Commonly used radioactive substances are Cesium (^{137}Cs), Cobalt (^{60}Co), Iodine (^{131}I), Phosphorus (^{32}P), Gold (^{198}Au), Iridium (^{192}Ir), Yttrium (^{90}Y), Palladium (^{103}Pa). The units of measurement for radiation include the *roentgen, radiation absorbed dose (rad),* the generation of oxygen free radicals, which degrade tumor DNA. Other units of radiation are the gray (Gy) and the Sievert (SV). Two general techniques of radiation delivery are used: brachytherapy and teletherapy. With brachytherapy, the radiation source is placed close to or within the target tissue. Teletherapy delivers radiation from a device outside the body. The accuracy of delivery is also enhanced by supervoltage radiation. A radioactive substance may be injected into a vein to travel to the cancer, for example radioactive iodine, which is used in treatment of thyroid cancer, or radioactive implants, which may be placed directly into the cancer. A linear accelerator directs the radiation to the tumor, while normal tissue is shielded as much as possible. A doctor tries to accurately target the radiation therapy to protect normal cells. For treating superficial skin lesions, the electron beam is used. Cells with low sensitivity are more resistant to the effects of radiation, but can, with sufficiently high dosage, be killed. However, high radiation doses may damage adjacent normal tissue. Therefore, radiation therapy is divided into a series of doses with moderate doses of radiotherapy or multiple beam paths over a prolonged period of time, which increases the lethal effects of the radiation on tumor cells, while decreasing the toxic effects of the radiation on normal cells, thus reducing the acute toxicity without compromising anti-tumor efficacy. Also normal cells have the capacity to repair themselves quickly after being exposed to radiation (Dow and Hilderley, 1992; Milenic and Brechbiel, 2004).

Physicians evaluate four factors when considering the treatment of cancer with radiotherapy: 1) tumor location - radiation may pose problems if a tumor is located on or near a vital organ that is particularly sensitive to radiation (eg, spinal cord), 2) extent of the tumor- benefit from radiotherapy may be limited if a tumor is too large or widespread, 3) patient health- a debilitated patient may be a poor risk for radiotherapy, and 4) therapeutic ratio (TR) - defined as the relationship between normal tissue tolerance dose and the tumor lethal dose. Radiation therapy plays a key role in curing many cancers particularly localized tumors, including Hodgkin's disease, squamous cell cancer of the head and neck, cancer of the skin, cervix, endometrium, breast, larynx, seminoma (a testicular cancer), prostate cancer, early-stage breast cancer, lung cancer, and medulloblastoma (a brain or spinal cord tumor). One could not effectively control numerous sites of metastases, because one would not be able to safely radiate such large areas. Lymphoma is usually not treated with surgery and chemotherapy, the radiation therapy is the treatment of choice. It may also be used to provide temporary relief of symptoms particularly in advanced cancer, or to treat malignancies (cancers) that cannot be removed with surgery as in multiple myeloma and advanced lung, esophageal, head and neck, and stomach cancers. It can be given as palliative therapy to relieve symptoms caused by spread of cancer to bone or brain. Often it is used to shrink the tumor as much as possible before surgery to remove the cancer. After surgery it is used to prevent the cancer from coming back. New techniques of intense and highly focused radiation therapy, such as proton radiation, can effectively treat certain tumors in areas where damage

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to normal tissue is a worry, such as the eye, brain, or spinal cord. Radiation may be preferred in patients who are high-risk surgical candidates. It is also the treatment of choice for most tumors of the CNS, because of the inaccessibility of these lesions to surgical procedures. In conjunction with surgery, radiation should be used when it can improve the local and regional control rate or the overall cure rate. In this respect, as in the case of many head and neck cancers, radiotherapy is used pre-operatively to reduce the tumor mass, or post-operatively to destroy residual cells. This approach has led to significant improvement in local control and cure of soft-tissue sarcomas.

Chemotherapy or drug therapy: Chemotherapy involves the use of drugs (chemical agents), that kill rapidly growing cells, to destroy cancer cells. It is followed for cancers of systemic sites. Those cancers that are the most rapidly growing (Burkitt's lymphoma, acute leukemia, germ cell cancer, and several others) may be cured by chemotherapy in many cases. Effectiveness of chemotherapy depends on that a tumor consists of rapidly dividing cancer cells and these cells are more sensitive to anticancer drugs than non-dividing, normal cells. Although an ideal chemotherapy drug would destroy cancer cells without harming normal cells, few such drugs exist. Cancer chemotherapy kills or arrests the growth of cancer cells by targeting specific parts of the cell growth cycle. However, normal healthy cells share some of these pathways, and thus are also injured or killed by chemotherapy. Thus toxicities occur with chemotherapeutic drug treatment, which tend to harm dividing normal cells, such as those found in the bone marrow or the lining of the gastrointestinal tract. Most chemotherapeutic agents act by damaging deoxyribonucleic acid (DNA), the cellular genetic material. In many cases, it is likely that drug cytotoxicity involves multiple intracellular sites of action and may not be linked to specific cell cycle events. Therapeutic index of a drug reflects the difference between its efficacy (tumor cell killing) versus its toxicity to normal cells. Classic chemotherapeutic drugs such as alkylating agents can be quite toxic and the number of cycles that may be administered is limited. Not all cancers respond to chemotherapy. The type of cancer determines which drugs are used, in what combination, and at what dose. Chemotherapy may be used as the sole treatment or combined with radiation therapy and surgery (Crowell, 2005).

Chemotherapy may be administered with curative or palliative intent, depending on the type and stage of the tumor. For example, testicular cancer, Hodgkin's disease, certain leukemias, diffuse non-Hodgkin's lymphomas, Ewing's sarcoma, and Wilms' tumor are now curable with chemotherapy alone. However, in patients with other types of advanced incurable diseases (eg. disseminated breast cancer), chemotherapy (including hormonal therapy) may provide years of effective palliation. Just as bacteria may develop resistance to antibiotics, cancer cells may become resistant to chemotherapeutic agents (Gatti and Zunino, 2005). Using several drugs at the same time (combination chemotherapy) is one way to minimize such resistance. Dose-intensity chemotherapy is a new but risky approach in which especially high doses of drugs are used. This therapy is used for a few types of cancer (including some types of myeloma, lymphoma, and leukemia) that have recurred even though the person had a good response when first treated with drugs. The strategy is to markedly increase the drug dose to kill more cancer cells and thus prolong the person's survival. However, it can cause life-threatening injury to the bone marrow. Therefore, it is commonly combined with bone marrow rescue strategies, in which marrow cells are harvested before the chemotherapy and returned to the person after chemotherapy.

Goal of cancer drug development is to find agents that are effective at killing tumor cells while sparing normal cells in the process. An exciting and very promising new area of cancer drug development is the identification of molecular targeted therapies (Thiery-Vuillemin *et al.*, 2003). Driven by increased knowledge of cancer cell biology, new agents are being designed to inhibit specific cellular proteins and signal transduction pathways. These are more specifically targeted at growth pathways that are only found in cancer cells and may be more effective while also being less toxic. These "molecularly targeted" drugs can enter cancerous (malignant) cells and interrupt important pathways of information flow in the cell, and thus render the cells defective, and they die, while avoiding undesirable toxicity. Imatinibsome, the first such drug, alters the energy site in the malignant cell and is highly effective in chronic myelocytic leukemia and certain tumors of the digestive tract. Other such drugs target cell surface receptors in nonsmall cell lung cancer and colon cancer. Some of these new targeted drugs have shown remarkable activity such as Gleevec for chronic myeloid leukemia (CML) and bevacizumab, which inhibits tumor blood vessel formation (angiogenesis). Further development of targeted therapies will be acheived as the knowledge continue to be explored that which pathways and systems are dysregulated in each type of cancer. These insights will usher in a new age of cancer treatment based on "individualized" therapy. These new

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molecules have anticancer activity when used alone, but are often more effective when combined with traditional, cytotoxic chemotherapy.

Chemotherapy Drugs

Alkylating agents: Cyclophosphamide, Chlorambucil, Melphalan : Forms chemical bond with DNA, causing breaks in DNA and errors in replication of DNA.

Antimetabolites: Methotrexate, Cytarabine, Fludarabine, 6-Mercaptopurine, 5-Fluorouracil : Block synthesis of DNA.

Antimitotics: Vincristine, Paclitaxel, Vinorelbine: Block division of cancer cells.

Topoisomerase inhibitors: Doxorubicin, Irinotecan : Prevent DNA synthesis and repair through blockage of enzymes called topoisomerases.

Platinum derivatives: Cisplatin, Carboplatin : Form bonds with DNA causing breaks.

Biotherapy: Biotherapy includes immunotherapy and biologic response modifier (BRM) therapy to enhance endogenous immune cell killing and tumor vaccines (Rieger, 1995; Rosenberg, 1997).

Immunotherapy: Even when a cell becomes cancerous, the immune system is thought to be able to recognize it as abnormal and destroy it before it replicates or spreads. So, the purpose of immunotherapy is to stimulate the body's immune system against cancer. Several approaches are used to stimulate the immune system to recognize and attack tumor cells. These include: 1) the use of vaccines developed from tumor cell fragments to "immunize" patients against their own tumors; 2) general (nonspecific) stimulation or restoration of immune function, as with interferon, levamisole, or the *Mycobacterium* BCG; and 3) the injection of the patient's own cytotoxic lymphocytes cultured for enhanced antitumor effects *in vitro* (adoptive biotherapy). Thus, a number of different approaches are being developed to utilize biotherapy in the treatment of human cancer. Use of vaccines is composed of antigens derived from tumor cells to boost the body's production of antibodies or immune cells (T lymphocytes). Its basis is that cancer cells possess distinct surface protein antigens that are potential targets for antibody-directed or cell-mediated immunity. When a cell becomes cancerous, new antigens, unfamiliar to the immune system, appear on the cell's surface (tumor antigens). The immune system may regard these new antigens as foreign and may be able to contain or destroy the cancerous cells by the immune mechanism and is often able to destroy cancerous cells before they can become established. However, even a fully functioning immune system cannot always destroy all cancerous cells. And, once cancerous cells reproduce and form a mass of cancerous cells (tumor), the body's immune system is highly unlikely to be able to destroy it. Thus, antibodies against the tumor antigens can be produced, but are usually not powerful enough to control the cancer. Substances such as extracts of weakened tuberculosis bacteria, which are known to boost the immune response, have been successful when applied locally to bladder cancers. Marek's disease virus (MDV), caused by a Herpesvirus, which causes polyneuritis and malignant lymphoma in poultry, is the only virus for which a vaccine is available to control cancer. To date, other vaccines have not proven useful in the treatment of cancer. Monoclonal antibody therapy involves the use of experimentally produced antibodies to specific proteins on the cell surface. These are administered to the cancer patient in an attempt to destroy tumor tissue. The monoclonal antibodies (MoAbs) can be used therapeutically when linked to cancer drugs, therapeutic radionuclides or potent plant toxins, such as ricin. The antibody binds to the cancer cell, selectively delivering the cancer drug or toxin to the tumor, called the magic bullets. Antibodies linked to a radioactive isotope can be used to deliver radiation directly to the cancer cells. This area of research is certain to expand, especially with the emerging availability of non-rodent (humanized) antibodies, which have much lower sensitizing side effects (i.e., fewer human anti-mouse antibody or "HAMA" reactions). Approaches for stimulating the host immune response is often used in patients with advanced cancer, which have depressed immune responses (Reiche *et al.,* 2004; Li *et al*., 2005; Stern and Herrmann, 2005).

Biologic response modifiers: These are used to improve the immune system's ability to find and destroy cancer cells, such as by stimulating normal cells to produce chemical messengers (mediators). **Interferon** (of which there are several types) is the best-known and most widely used biologic response modifier. Almost all human cells produce interferon naturally, but it can also be made artificially using recombinant technology. With interferons measurable responses have occurred in people with Kaposi's sarcoma, chronic myelocytic leukemia, renal cell carcinoma and malignant melanoma. Two of the most frequently used biotherapy agents are α-IFN (alfa interferon) and interleukin-2 (IL-2). α -IFN produces antitumor effects by several mechanisms: 1) inhibition of protein synthesis (one of its main antiviral effects), 2) enhanced antigenicity of tumors by up-regulation of the major histocompatibility complex (MHC) on the cell surface, and 3) general immune stimulation

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to increase the activity of effector cells such as cytotoxic T-lymphocytes (CTL). α -IFN is given by self-administered subcutaneous injection, usually three times weekly. IL-2 is a polypeptide growth factor for T lymphocytes, Its normal function is to increase T cells following antigen presentation on a macrophage. In cancer therapy, IL-2 has been shown to increase the numbers and activity of specialized cytotoxic T-cells called lymphokine activated killer (LAK) cells. These cells mediate direct tumor cell lysis by releasing toxins next to the target tumor cell. A more specialized type of LAK cell is the tumor-infiltrating lymphocyte or TIL, which is found within tumor masses. This cell has even greater tumor-lytic activity. When cultured *in vitro* with a patient's own lymphocytes, IL-2 has been used as a stimulant of LAK cell formation. These cells can then be reinfused into the patient, a process called "adoptive transfer" or adoptive nonspecific biotherapy.

Hormonal/Endocrine Therapy: The rationale for hormonal therapy is that some cancers arise from tissues sensitive to hormonal growth control (eg. breast, prostate, endometrium and liver) and retain this sensitivity, even after malignant changes. Endocrine therapy deprives the tumour cell of hormones either by reducing local and systemic hormone concentrations or by blocking its receptor. Whether a tumor will respond to a hormone depends on the presence of receptors for that hormone in the tumor tissue. For example, breast cancers with high estrogen receptor content have a high likelihood of responding to anti-estrogen therapy with tamoxifen. Other agents are like progestins (megestrol), estrogens (diethylstilbestrol), glucocorticosteroids (prednisone), Imatinib etc. These agents tend to reduce symptoms (palliation), but not complete shrinkage or eradication of disease. Nonetheless these responses can be long lasting. The growth of a hormone-sensitive tumor often may be "turned off" for many months by hormonal therapy. Because of its relative lack of toxicity, endocrine therapy is widely used to treat advanced disease as adjuvant and preoperative therapy, and is now being assessed for disease prevention. Hormonal agents may be natural or synthetic. Several of the newer hormonal agents are synthetic peptides which mimic endogenous peptide hormones. For example, there are several analogs of gonadotropin releasing hormone (GnRH) which act at the pituitary to reduce the release of sex hormones, FSH and LH. This deprives the prostate gland of its androgen stimulation (a medical castration) without the need for surgery. A number of tumors have been shown to be responsive to biotherapy, although complete responses are rare and overall response rates are low. Hormone-responsive tumors are breast cancer, prostrate cancer, neuroendocrine gut tumors, lymphocytic leukemia and lymphomas, endometrium and liver cancers.

Thermotherapy: It utilizes the principles of cryotherapy and heat.

Recent evidence has shown cancer cell growth and viability is dependent upon proper telomere maintenance, which contributes towards the indefinite proliferation of cancers and that targeting telomere maintenance mechanisms and inducing telomere dysfunction in cancer cells by inhibiting telomerase can lead to catastrophic events including rapid cell death and increased sensitivity to other cancer therapeutics. Therefore, preventing the maintenance of telomeres, such as via telomerase inhibition or loss of t-loop, and thus the immortal phenotype of cancer might be a useful mode of therapy. This might provide a mechanism or a window of opportunity to specifically target and inhibit the growth of cancer cells. The differences in telomerase length, coupled with the much more rapid rate of cell division in cancer cells, make the inhibition of telomerase a potential cancer therapeutic target. Thus the limitless proliferative potential of cancer could be blocked. Short telomeres have been recently suggested to be a potential cancer predisposition factor. Ascertaining the telomere length status may be useful in screening patients for telomerase inhibitor therapies. Thus, it might be possible to use telomere lengths to identify high-risk groups for preventative cancer therapies. Combining telomerase inhibitors with conventional cancer therapies or using inhibitors to prevent tumor re-population might prove to be a useful cancer treatment regimen. By allowing critically short or uncapped telomeres to be recognized as DNA breaks, additional DNA damage signals in the mitotically unstable cancer cells can trigger the ultimate mitotic catastrophe of apoptosis or terminal growth arrest. It will be necessary to see their positive potential translated into clinical trials (Gilley *et al.*, 2005).

Each treatment method has a unique place and value in the treatment of cancer. For example, surgery can control or cure tumors that can be entirely removed from surrounding normal tissues; radiation therapy can control or cure certain cancers confined to a limited area, sometimes avoiding deforming surgery; chemotherapy can be used to cure or control metastatic malignancies; biotherapy is used to manipulate the immune system to help the body fight cancer or to administer biotherapeutic agents in an attempt to destroy tumor tissue. Frequently, combinations of these methods are used because some cancers are more effectively treated by combinations than by any one of these methods alone.

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Combined-Modality Therapy: Multimodality therapy combines the assets of various modes of cancer treatment. For some cancers, the best approach is a combination of surgery, radiation, and chemotherapy. Surgery or radiation therapy treats cancer that is confined locally, while chemotherapy also kills cancer cells that may have spread. Sometimes radiation or chemotherapy is given before surgery to shrink a tumor, thereby making the complete removal of the tumor using surgery more likely, or after surgery to destroy any remaining cancer cells. The stage of the cancer often determines whether single therapy or a combination is needed. For example, early-stage breast cancer may be treated with surgery alone or surgery combined with radiation therapy, chemotherapy, or with all three treatments, depending on the size of the tumor and the risk of recurrence. Locally advanced breast cancer is usually treated with chemotherapy, radiation therapy, and surgery. Sometimes combination chemotherapy is used not to cure but to reduce symptoms and prolong life. This can be useful for people with advanced cancers that are not suitable for irradiation or surgical treatment, for example, those with nonsmall cell lung cancer, esophageal cancer, or bladder cancer. Commonly several chemotherapy drugs are combined (combination chemotherapy), so as to use drugs that work on different parts of the cancer cell's life cycle, thereby increasing the likelihood that more cancer cells will be killed. Here each drug can be used at its optimal dose, helping avoid intolerable side effects. Drugs that kill tumor cells may be combined with antibodies or with drugs that stimulate the body's immune system against cancer (biologic response modifiers). Adjuvant chemotherapy is used following or in conjunction with some other primary therapy. It is designed to eradicate disseminated micrometastases that remain after surgery and/or irradiation of the primary tumor. It is practised in patients with breast cancer, osteogenic sarcoma, large bowel cancer, ovarian cancer, head and neck cancer, pancreatic cancer, melanoma, and nonsmall cell lung cancer.

The goals and progress of cancer therapy can be clarified by observing the success of cure. For a potential cure, a complete remission or complete response must be achieved, which requires disappearance of clinically evident disease. Absence of all evidence of a cancer after treatment is termed as remission. Such patients may appear to be cured but may still have viable neoplastic cells that will, in time, cause relapse or recurrence of cancer, where the cancerous cells return after treatment, either in the primary location or as metastases (spread). A partial response is a > 50% reduction in the size of a tumor mass or masses, which may lead to significant palliation and prolongation of life, but tumor regrowth is inevitable. A patient may also have no response. The interval between disappearance of cancer and relapse is termed the disease-free interval or disease-free survival.

Side Effects of Cancer Therapy:

Almost everyone who receives cancer treatment experiences side effects, which vary according to the treatment and the area of the body undergoing treatment. Chemotherapeutic agents, sometimes called cytotoxic agents because they kill cells, produce toxic side effects on rapidly dividing host tissues such as bone marrow and intestinal mucosa. Some normal cells, including blood cells, hair, and cells lining the gastrointestinal tract are also rapidly dividing, and are most likely to be damaged. All chemotherapy drugs affect normal cells and cause side effects, varying according to the type of drug. Chemotherapy commonly causes nausea, vomiting, loss of appetite (anorexia), weight loss, fatigue, and low blood cell counts that lead to anemia and risk of infections. People often lose their hair. Cytopenia, a deficiency of one or more types of blood cell like abnormally low numbers of red blood cells (anemia), white blood cells (neutropenia or leukopenia), or platelets (thrombocytopenia), can develop because of the toxic effect of drugs on bone marrow. These drugs also can cause nerve dysfunction, heart and kidney damage, hearing loss, bone marrow suppression, injure lining of stomach and decreased fertility. Cytotoxic chemotherapy has an independently negative effect on bone cells (primarily osteoblasts) and can induce premature ovarian failure in patients with breast cancer, which leads to estrogen deprivation, which in turn leads to loss of bone mineral density (BMD). Radiation therapy is also associated with a significant number of adverse reactions, which depend on the part of the body being irradiated, how large an area is being treated, the dose and schedule given, and the tumor's proximity to sensitive tissues. It can damage normal tissues adjacent to the tumor, especially tissues in which cells normally divide rapidly such as skin, the bone marrow, hair follicles, and the lining of the mouth, esophagus, and intestines. Radiation can also damage the ovaries or testes. Skin and hair are most noticeably affected by radiation treatment, resulting in skin lesions, burning, redness, and possibly hair loss. The most common complaints are fatigue, malaise, anorexia, decreased libido, hair loss, mucositis, and bone marrow depression. Others are low blood counts, difficult or painful swallowing, erythema, edema, desquamation (shedding

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or sloughing-off of the outer layer of skin), increased skin pigment (hyperpigmentation), atrophy, skin itching (pruritus), skin pain, changes in taste, lack of appetite, nausea, vomiting, gastritis/enteritis, diarrhea. fetal damage (in a pregnant woman) and increased susceptibility to infection. Acute adverse reactions occur within the first few weeks of treatment and subside after a few weeks. These effects are more severe with higher doses or the concomitant use of chemotherapy. Subacute adverse reactions develop within weeks to 6 months after radiotherapy, like the radiation pneumonitis. Late adverse reactions appear months or even years after therapy, depending on the total radiation dose, and are usually caused by damage to vascular or connective tissue, like fistulas, fibrosis, necrosis, edema, and secondary neoplasms. Late complications are not usually spontaneously reversible and they do not generally respond to treatment.

Hormonal therapies can cause endometrial cancer, blood clots, hot flashes, erectile dysfunction (impotence), abnormal liver function test and fluid retention. These therapies, such as selective estrogen replacement modulators (SERMs) and aromatase inhibitors have been shown to cause bone loss in premenopausal women with breast cancer. Androgen deprivation therapy may cause hypogonadism, which increases risk for fracture. Monoclonal antibodies can cause allergic reaction. Biologic response modifiers can also show toxicity, alpha-IFN produces a flu-like syndrome (headache, fever, chills, respiratory distress, myalgia and bone marrow suppression. The toxicities of IL-2 are more serious and include a flu-like syndrome along with significant fluid accumulation, which can lead to renal or cardiac insufficiency. Cancer therapy can also cause lactose intolerance and mouth ulcers. Some cancer treatments cause “dumping syndrome” i.e. food is “dumped” into the jejunum (small intestine) 10 or 15 minutes after being swallowed and the presence of undigested food in the jejunum leads to abdominal fullness, nausea and crampy abdominal pain. Other symptoms include feeling warm, dizzy, and faint and there can be rapid pulse and cold sweats immediately after eating. Bone loss also can be caused by cytotoxic therapy directed toward the tumor or by surgical or hormonal therapy leading to estrogen or androgen depletion. This is referred to as treatment-related osteoporosis or cancer-treatment–induced bone loss (CTIBL). So it can be caused by glucocorticoids, gonadal ablation or suppression (ovarian and testicular), and radiation therapy to bone (causing osteonecrosis and reduced function and number of osteoblasts). Surgically induced menopause by oophorectomy will decline estrogen levels and produce negative bone health.

Seeing the several side effects of cancer therapies, preventive and corrective measures should be followed in cancer treatment. Careful doses of treatment modalities are required in well monitored hospital settings. Relieving side effects is an important part of treatment. Symptomatic treatment can be given for some of the side effects. A registered dietitian, which is a trained health professional in the area of nutrition, can assist in nutritional planning for people with cancer.

PREVENTIVE MEASURES

Reducing the risks of certain cancers may be possible through certain dietary and other lifestyle changes. The risk of malignant tumors can be reduced by not smoking or chewing tobacco, avoiding heavy alcohol consumption, eating a healthy diet, exercising regularly, maintaining a healthy weight, reducing sun exposure if you burn easily, and minimizing exposure to radiation and toxic chemicals. The idea is that tumors can be prevented by avoiding things that cause cancer. Not smoking and avoiding exposure to tobacco smoke can greatly reduce the risk of lung, kidney, bladder, and head and neck cancer. Avoiding the use of smokeless tobacco (snuff, chew) decreases the risk of cancer of the mouth and tongue. Avoiding sun exposure (especially during the middle of the day) can reduce the risk of skin cancer. Covering exposed skin and using sunscreen lotion with a high sun protection factor (SPF) against ultraviolet light also helps reduce the risk of skin cancer. A reduced intake of fat, particularly from animal sources, in the diet appears to decrease the risk of breast and colon cancer. Use of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) reduces the risk of colon cancer. Avoiding occupational carcinogens (for example, asbestos), increasing intake of fruits and vegetables, being physically active and maintaining a healthy weight are good preventives measures.

COMPLEMENTARY / ALTERNATIVE MEDICINE (CAM)

As the popularity of complementary/alternative medicine (CAM) grows, patients are incorporating more CAM therapies into their conventional cancer care. Some people turn to alternative medicine including certain medicinal herbs to treat their cancer, instead of or in addition to standard treatment. However, most types of alternative medicine have not been subjected to careful scientific studies. Very little is known about the effectiveness of alternative medicine in treating cancer. It is generally believed that the use of alternative medicine may be toxic, may interact with standard

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treatment, thus reducing the effectiveness of chemotherapy, it may be costly, reducing the person's ability to afford standard treatment. Therefore these points have to be clarified via scientific basis and practical implications / clinical trials. Of these Ayurvedic medicine, herbal products, homeopathy and cow urine therapy can share the high standards of medicine. In the next section of this review, cow urine therapy will be discussed in details (Treasure, 2005).

COW URINE THERAPY

Cow urine has been described in 'Sushrita Samhita' and 'Ashtanga Sangraha' to be the most effective substance/secretion of animal origin with innumerable therapeutic values. The medicines made from cow urine are used to cure several diseases. Taken in measured quantities, cow urine or gaumutra has a unique place in Ayurveda and is suggested for improving general health. Exploring its antimicrobial activities, it is being used to produce a whole range of Ayurvedic drugs. Cow urine therapy has a long history. It is recognized as 'water of life' or "Amrita" (beverages of immotality), the nector of the God in Vedas, sacred Hindu writing, which is said to be the oldest books in Asia. In India, drinking of cow urine has been practiced for thousands of years. It is an important ingredient of panchgavya, which has been tested by various workers for its immunomodulatory properties and have been reported that it enhances both cellular and humoral immune response (Kumar, 2001; Chauhan *et al.,* 2004). It has also been experimentally proved that among all sorts of urines, the urine of the Indian cows is most effective and interestingly almost nil or few medicinal properties with regards to immunomodulation are present in the urine of crossbred, exotic cows and buffaloes. The immunomodulatory property of indigenous cow urine is due to the presence of a "Rasayan" which has been found absent in urine of other animals on HPLC analysis

Cow urine singularly has got all such chemical properties, potentialities and constituents that are capable of removing all the ill effects, imbalances in the body (Bartnett, 1988; Chauhan *et al.,* 2001; Chauhan, 2003a). Cow urine contains 24 types of salts. Its main contents are water 95%, urea 2.5%, minerals, salt, hormones, and enzymes-2.5%. It contains iron, calcium, phosphorus, carbonic acid, potash, nitrogen, ammonia, manganese, iron, sulphur, phosphates, potassium, urea, uric acid, amino acids, enzymes, cytokine and lactose etc. (Bhadauria, 2002). Copper has the power to destroy diseases and act as an antidote. Cytokines and amino acids might play a role in immune enhancement. Since the urine of the cow contains all beneficial elements in it, hence it is natural and universal medicine that fulfills the deficiency of elements and reduces the increased elements in the body. It is the unique quality of the urine, which helps in curing even the most incurable diseases. There is evidence that the urine of the cow works as the best appetizer. It smoothens and nourishes the heart and adds to the power of wisdom of man, and increases their physical strength as well. It increases life span and purifies blood from all sorts of impurities. Cow urine is entirely sterile after secretion and has antiseptic effect. It acts like a disinfectant and prophylactic agent and thus purifies atmosphere.

Practitioners of Ayurvedic medicine (from India) routinely use urine as a remedy. A number of ailments could be treated by cow urine therapy. Most of the medicines are made by distilling urine and collecting vapours termed as 'ark' (distillate). Improvements have been shown or reported with those suffering from flu, sinus, allergies, colds, ear infection, rheumatoid arthritis, bacterial/viral infections, tuberculosis, chicken pox, hepatitis, leprosy, asthma, gastric ulcer, heart disease, depression, hypertension, fatigue, burns, skin infections, eczema, tetanus, morning sickness, fever, obesity, etc. It is also used as a diuretic, laxative and for treatment of chronic malaria, enteritis, constipation, edema, baldness, headaches, fever, chemical intoxication, aging etc. It is proved as a universal curer of blood disorders, leucorrhoea and even leprosy. The urine of the cow cleans the intestines and removes the deposited material. Hence diseases like fever, mouth and skin diseases menstruation disorders, asthma, giddiness, increase of cough and urinary irregularities in humans are cured by its regular use without any side effects. It is non-toxic in nature. Cow urine can kill the number of drug resistant bacteria and viruses. Even this therapy has been reported to be beneficial for dreaded diseases like cancer, AIDS and diabetes.

Cow Urine as Immunostimulant

Cow's urine has immunostimulant activity in plants and animals. Recent researches showed that cow urine enhances the immune status of an individual through activating the macrophages and augmenting their engulfment power as well as bactericidal activity. In poultry, cow urine has been reported to enhance the immunocompetence of birds and provide better protection along with vaccination and increases egg production and egg quality. *In-vivo* cow urine treatment to developing chicks marginally upregulated the lymphocyte proliferation activity (Prabhakar *et. al.,*

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2004). Chauhan *et al.* (2001) and Kumar *et al.* (2004) reported the cow urine (Kamdhenu ark' / cow urine distillate) to be a potent and safe immunomodulator, which increases both humoral and cell mediated immunity in mice. It was observed that cow urine enhances both T and B cell proliferation and also increases the titre level of IgG, IgA and IgM antibodies. Chauhan *et al.* (2004) observed that it increases the secretion of interleukin-1 and 2 also. The level of both IL-1 and 2 in mice got increased by 30.9 and 11.0%, respectively and in rats these levels were increased significantly by 14.75 and 33.6%, respectively. Prabhakar (2004) reported that the cow urine had protective effect on lymphocytes of birds undergoing apoptosis and suggested the exploitation through experimental trails for specific use of cow urine as an adjunct to vaccination. Thus the cow urine not only maintains the immunity of body but also modulate it in the positive direction to an optimum level. Garg *et al.* (2004) reported beneficial effects of cow urine on serum biochemical profile (total serum protein, glucose, calcium and cholesterol of laying birds. Its usefulness as antimicrobial agent, positive effect on body weight gain and haematological profiles have also been reported. Garg *et al.* (2004) suggested that cow urine can be used as a feed additive for layer birds in order to get good quality eggs and immune-enhancer.

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Cow urine as Bioenhancer

A cow urine distillate fraction (ark) has been identified as a bioenhancer of the activities of commonly used antibiotics, anti-fungal and anti-cancer drugs. Recently the cow urine has been granted U.S. Patents (No. 6896907 and 6410059) for its medicinal properties, particularly for its use along with antibiotics for the control of bacterial infection and fight against cancers. The activity of Rifampicin, a front-line anti-tubercular drug used against tuberculosis, increases by about 5-7 folds against *E. coli* and 3-11 folds against Gram-positive bacteria (The Hindu, 4 July, 2002; The Indian Express, 4 July, 2002). Bioenhancers are substances, which do not possess drug activity of their own but promote and augment the bioactivity or bioavailability or the uptake of drugs in combination therapy. Such bioenhancers have been earlier isolated only from plant sources. It has now been found that cow urine also acts as a bioenhancer and increases the efficacy of the antibiotics against infectious agents. The molecule of invention helps in the absorption of antibiotics across the cell membrane in the animal cells, gram positive and gram negative bacteria. Bioenhancement has also been observed with other drugs viz. Ampicillin, Isoniazid, Clotrimazole, Cyanocobalamine etc. Bioenhancer activity has been found to reduce the antibiotic dose per day and duration of treatment in tuberculosis patients (Joshi, 2002). The Indigenous cow urine contains "Rasayan" tatva, which is responsible to modulate immune system and act as bioenhancer.

ANTI-CANCER PROPERTIES OF COW -URINE

Cow urine possesses anti-cancer properties. Research works carried out by Go-Vigyan Anusandhan Kendra (Cow Science Research Center) at Nagpur revealed the beneficial properties of cow urine in the treatment of cancers. Further extensive research on cow urine therapy against fighting cancer carried out by Scientists of Central Institute of Medicinal and Aromatic Plants (CIMAP), CSIR Center at Lucknow, along with collaboration with Go-Vigyan Anusandhan Kendra, Nagpur confirmed this milestone achievement. Studies highlight the role of cow urine in curing cancers and that cow urine enhances the efficacy and potency of anti-cancer drugs. Recently, this significant achievement has been validated by the grant of U.S. Patent (No. 6896907) in the field of treatment of cancers (Amar Ujala, July, 19, 2005).

Scientists have proved that the pesticides even at very low doses cause apoptosis (cell suicide) in lymphocytes of blood and tissues through fragmentation of DNA. Distilled cow urine protects DNA and repairs it rapidly as observed after damage due to pesticides (Ambwani, 2004). It protects chromosomal aberrations by mitocycin in human leukocyte (Datta, 2001). Cow urine helps the lymphocytes to survive and not to commit suicide (apoptosis). Kumar *et al.* (2004) reported the prevention of pathogenic effect of free radicals through cow urine therapy. These radicals cause damage to various tissues and attack enzymes, fat and proteins disrupting normal cell activities or cell membranes, producing a chain reaction of destruction leading to the ageing process of a person. By regular use of cow urine one can get the charm of a youth as it prevents the free radicals formation.

Thus, the cow urine therapy is suggested to possess potent anti-cancer abilities by the virtues of the following properties –

Antimicrobial capability: Cow urine can kill the number of drug resistant bacteria and viruses, thus can reduce the incidences of cancer since many a viruses have been reported to cause cancer.

Bioenhancing property: It can promote and augment the bioactivity or bioavailability or the uptake of cancerous drugs, thus could enhance the efficacy and potency of the chemotherapy drugs, and reduce

their dose and duration of treatment, which could also help reduce the cost and side effects of chemotherapy. So in combination therapy cow urine can be used efficiently.

Immunomodulating activity: Cow urine enhances the immunocompetence and improves general health of an individual. It has vital potential to enhance the activity of macrophages and lymphocytes (both T and B cells), and has been reported to increase the humoral and cellular mediated immunity. Increased immunocompetece of an individual is a very essential parameter to prevent the development of cancers by several mechanisms, of which the upregulation of lymphocyte proliferation and stimulation activity, increased macrophage activity, higher antibody production and increased synthesis and secretion of cytokines (IL-1, Il-2) plays significant role by enhancing the recognition of tumor cells by the immune cells of the body and cytotoxic activities of the tumor killing cells, the lymphocytes.

Anti-aging factor: It is an efficient anti-aging factor, since prevents the free radicals formation, which could help preventing cancers as the incidences of cancer increases as the one progresses towards old age.

DNA repairing potential: Cow urine efficiently repairs the damaged DNA, thus can be very effective for the cancer prevention and therapy, and can also reduce the spread of malignant cancers and help fighting tumors.

Apoptosis inhibitor: Cow urine can tremendously reduce apoptosis in lymphocytes and helps them to survive, thus the body can avail the tumor fighting abilities of the lymphoctyes at their optimum activity and survivabability.

US Patent for Cow urine in the field of cancer: Recently a pharmaceutical composition comprising an effective amount of bioactive fraction from cow urine distillate (CUD) as a pharmaceutically acceptable additive was tested and applied for a US patent. The invention relates to an absolutely novel use of CUD as an activation enhancer and availability facilitator for bioactive molecules such as anti-infective and anti-cancer drugs. It was found that the urine distillate effectively reduced the dosage of drug needed for the therapies. The applicants (Khanuja *et al.,* 2002) obtained the 'Kamadhenu Arka' (CUD) from Go-Vigyan Anusandhan Kendra, Nagpur, India and studied its effect and of the dried fraction (GM-IV). A pharmaceutical composition comprising of at least one anticancer agent ('Taxol'- Peclitaxel) and a cow urine distillate or a dried fraction (GM-IV) obtained from cow urine distillate was studied. Cow urine was distillated around 40-50°C to obtain the distillate and the distillate concentrate obtained by lyophilization. The cow urine distillate was used in a concentration range of 0.001µl/ml to 100µl/ml, and at a concentration 1µl/ml was found to enhance the cell division inhibitory activity of the drug 'Taxol' in breast cancer cell line, MCF-7 (NCCS, Pune) by 2-20 folds. The GM-IV which was obtained in the range of 10-20 grams/100ml of the distillate showed the same effect at 0.001-10µg/ml and was found to be more stable and devoid of unpleasant smell of urine and hence considered as the advanced product of the invention. Thus the potency of 'Taxol' (paclitaxel) was observed to get increase against MCF-7, a human breast cancer cell line in *in-vitro* assays.

Table showing the effect of Cow urine distillate as activation enhancer of 'Taxol'

Taxol (µg/ml)	Initial titre of cancer cells	Final titre of cancer cells with Taxol	Final titre of viable cancer cells with Taxol and Cow urine distillate
0.001	$0.9x10^6$	$0.059 x10^6$	$0.039 x10^6$
0.005	$0.9x10^6$	$0.042 x10^6$	$0.032 x10^6$
0.01	$0.9x10^6$	$0.036 x10^6$	$0.012 x10^6$

The most important feature of this invention is the finding that the enhancement action and effectiveness of the 'Arka' is achievable in the very low concentration (nano to micro molar levels), thus a very low dose of ark can be helpful in curing cancer, which can reduce the cost of the treatment.

Thus encouraging results were observed with cow urine treatment for the antibiotics as well as cancer therapy. The findings have reflected a direct implication in reducing the effective dose of drugs as well as acting as a bio-enhancer. Therefore, the future of cow urine therapy is encouraging especially in cancer therapy, and it may very well reduce the harmful side effects of radiation treatments. The above two U.S. Patents have attracted global attention. US Patents honored to Indian Scientists on Cow urine therapy also made realize that the traditional practices from Indian systems of medicine have a strong scientific base.

During the past few years cow urine therapy has provided promising and authentic results for the treatment of cancer, a deadly malady which is being faced by the mankind and the incidences of which are ever increasing in the current scenario of changed lifestyle and food habbits along with exposure to predisposing factors of carcinogens such as tobacco chewing, smoking, alcohol intake, environmental

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pollutants, occupational health hazards etc. Anti-cancer potential of cow urine therapy has been reflected by several case reports, success stories and practical feed back of patients for the treatment of cancer.

CASE REPORTS, FEEDBACK AND SUCCESS STORIES

Cow Urine Cancer Cure: Oro-Pharyngeal Carcinoma- A Case Report: A patient (63 old women) from Kasargod district of Kerala state in November 2003 was presented to Kasargod Institute of Medical Sciences, Kasragod, Kerala, with stage IV squamous cell carcinoma of tonsil, and was treated with radiotherapy. Even though the carcinoma of tonsil is highly sensitive to radiations, it is unable to cure the IVth stage. The presented patient showed nasal regurgitation, dysphagia, dyspnoea and was spitting blood at times. The patient was supposed to succumb to the tonsilar neoplasia as evinced by the cachetic appearance and the severity of the symptoms suggesting a poor prognosis. She was later adviced to take 15 ml of 'Amrutha Sara' (cow urine distillate) twice a day and was asked to come after 2 weeks for the follow up. On the first follow up visit the patient had shown improvement in the symptoms and was able to take small quantities of liquid food without the help of feeding tube. The same therapy was continued for a period of 10 months with which the patient was completely cured of the disease. After the cow urine therapy, the physical examination revealed no visible oropharyngeal lesions and no cervical palpable lymph glands. The malignant lesions in tonsils and secondary lesions in lymph glands were effectively controlled. The surface of the tosillar fossa and fauces were smooth and showed no evidence of tumor growth. The tonsillar malignancy disappeared completely which suggested the antineoplastic effects of cow urine distillate. This points to the possibility of the role of the 'Amrutha Sara' as an effective antineoplastic drug, clearly evinced by the dramatic recovery of the patient from stage IV of the cancer to normalcy. The antineoplastic effects of cow urine may possibly be due to the antioxidant properties of vitamins A, E, C and the volatile fatty acids, both of which acted together to elicit a favorable response.

Other Case Reports And Success Stories: In other case reports and feed back obtained from persons treated for cancer using processed cow urine in the form of 'Ark', it has been observed that cow urine therapy was successful in fighting the cancer as reflected by the absence of cancerous cells/tissue, decrease in the size of tumor, clinical and biochemical picture of the patient. Mr Kamlesh kumar Agarwal, a native of Kareli Dist. Narsinghpur (MP) suffered from a cancer near the kidney due to which his kidney became nearly non-functional and inspite of different known cancer-therapies, there was no improvement in his health. After the use of 'Kamdhenu Ark' prescribed by the Cowpathy physicians, Nagpur, 98% improvement was reported in his cancer. Mr. Ram Sagar Singh, a native of Begusaray, north bihar got 80% improvement in the throat cancer after cow urine therapy. Smt. Seema Verma , resident of Jainagar (north Bihar), was completely cured from brest cancer by taking kamdhenu ark. Mr. Babulal Rungta, got affected with cancer suffered from chronic renal failure, with serum creatinine and urea level being 10.4 and 107, respectively, and was kept on dialysis twice a week. After cow urine therapy (Kamdhenu Ark) his serum creatinine and urea levels were dropped down to 5.3 and 63, respectively with a drastic improvement in the functioning of kidneys and relieving of cancer. Mr. Nanak Bhosray Dhingra, a patient suffering from multiple myeloma and severe waist pain showed improvement with the cow urine therapy.

However, scientific validation of cow urine therapy for the prevention and treatment of cancer, as reflected in the above practical cases and reports, is required for its worldwide acceptance and popularity. The unique anti-cancer activity of cow urine needs immediate attention and the strategies for promoting its vital medicinal potential and perspectives for the benefit of mankind should be planned appropriately. For this proper support of the scientists, researchers and clinicians/ physicians is needed by which authentic research data and practical implications of cow urine therapy in the field of treatment of cancers can be generated, which can further strengthen this alternate low cost therapy having no side effects, generally observed with chemotherapy and radiation therapy being followed for curing cancers, and thus confidence can also be inspired in the public about its good virtues.

STRATEGIES TO PROMOTE COW-URINE THERAPY

- Comparative chemical, microbiological and immunological analysis of urine of various indigenous cattle breeds with special reference to their medicinal and nutritional significance should be evaluated scientifically.
- Integrated and coordinated approach should be made for promoting scientific outlook, research and applications of cow urine in the field of medicine through information sharing by organizing conferences, seminars,

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workshops, exhibitions and orientation programmes.

- A sound data-base or data-collection system should be developed for further scientific evaluation of cow urine in the treatment of cancer and other diseases including the incurable diseases like AIDS. There should be a drive for the verification of clinical and medicinal claims made in ancient literature related to medicinal properties of cowpathy.
- Applications of cow urine need to be testified in clinical trials in Veterinary Colleges, Research Institutes, Universities and Hospitals. Research programmes should be undertaken, encouraged and supported in national institutions, universities and non-government organizations (NGOs).
- Special R&D fund should be created to encourage both public and private sector institutions to undertake result-oriented and time-bound projects on cow urine.
- The drug control authorities should, after thorough examination, include such products in Indian pharmacopia so that their production and quality may be suitably standardized.
- Wide publicity by mass communication is needed by publishing literature, research/ popular articles, and launching web-site(s) on the implications of cow urine for treating several diseases and as a potent anti-cancer therapy. Centers should be established and recognized for promotion of the innovations in the field of utility of cow urine in treating cancer.
- Encouragements, rewards and honors should be given to research in cow urine therapy such as that done by the Govigyan Anusandan Kendra, Nagpur and CSIR at Lucknow and other centers, which led to the grant of U.S. Patents, and which may also help in generating alternative treatment methodologies.
- Proper attention should be given on cow urine and panchgavya therapy for inducing protection against several diseases in the livestock/poultry populations. The role of cow urine in enhancing the immunity and general health needs to be explored in the right directions.
- Subsidies should be given for production of cow urine distillate or ark in bulk quantities and its wide availability should be facilitated and strengthened.
- As source of medicinal benefits apart from mechanical, thermal, and electrical energy along with agricultural benefits, the cattle wealth should be promoted in the country.

By providing proper funds, infrastructure and needful promotional campaigns of publicity (advertisements, mass media awareness) and generating scientific data for the support of cow urine therapy in curing cancers, this alternative can come out to share shoulders with the allopathy and multi-national drug companies.

CONCLUSION

Cancer is a dreaded malady to the mankind, which though can be treated by following various therapy procedures of surgery, chemotherapy, radiotherapy and immunotherapy along with recent molecular approaches of gene therapy, but the success rate and cost of these therapy modalities is not very high and moreover, their well known side effects puts burden on the patients to be treated. Alternate therapies including of herbs, homeopathy and ayurvedic medicines have also been claimed to be helpful in the prevention and control of cancer. Cow urine therapy has also been claimed to possess anti-cancer properties and has been supported recently by the grant of US patent in the field of cancer treatment by its virtues of bioenhancing the activity of anti-cancer drugs. The hypothesis of cow urine therapy in curing cancer has also been supported in the last few years by the case reports, feed backs and success stories of the patients treated by this novel alternate therapy for cancer. The area of cow urine therapy has tremendous potential in the field of medicine and has not been exploited to the extremes. Efforts need to be made for public awareness about the vital virtues of cow urine therapy. Though, the end user claims are many but scientific validation of those claims is required. Most of the tested practices of cowpathy or cow urine therapy are rejected as myth or mythological adventures. Now people need information and data based on research. It is therefore necessary to blend science, spirituality and wisdom. Such a blending has resulted in US patents for the cow urine in possessing anti-cancer and bio-enhancing properties. These approaches and their potential applications should be widely promoted. Modulating into the right channels the research on cow urine and other panchgavya elements, may be many more patents are awaiting ahead. Grant of U.S. Patents to cow urine has given the ultimate stamp of approval for Indian Systems of Medicine and

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the panchgavya products, particularly the cow urine, since they have passed through the high standards of modern scientific testifying methodologies. Establishment of research and development centers in this medicinal utility of cow urine and generation of authentic data for the support and of cow urine therapy in the treatment of cancer by physicians, clinicians, scientists and researchers should be given priority, which can strengthen and promote this unique and natural alternate therapy in fighting against the cancer, which would provide a great relief to the human sufferings. Cow urine is a universal medicine and can be the best therapy for mankind in curing various sorts of disorders. It is non-toxic and can be obtained free of cost trough domestication of indigenous cow. The cow urine therapy should gain popularity not only in traditional families but also in highly educated and scientific societies. Thus an integrated approach is necessary to promote the highly valuable virtues and wide applications of Cowpathy, a new version of ancient science, which is definitely a promising formulation in the years to come by following the desired promotional strategies. Utilizing the beneficial properties of cow urine, day may not be far away when the incurable diseases like cancer, AIDS and other deadly maladies can be treated successfully. The role of cow urine in curing the cancer needs further attention as they can serve as a reliable treatment alternative without side effects. Further case studies involving the successful use of 'Go-muthra Ark' or 'Kamdhenu Ark' are to be brought to medical attention and should be passed on to the masses.

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