

History of Cancer

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Many believe that human cancer is probably as old as the human race. There is plenty of evidence from paleopathology to suggest that cancer appeared much before the human race appeared on this planet. Earliest evidence of cancer is found in fossilized dinosaur bone dating back to 70 million years. Researcher Bruce Rothschild and colleagues of the Northeastern Ohio University College of Medicine in Rootstown studied over 10,000 dinosaur vertebrae from 700 museums across North America. They studied several families of dinosaurs including Stegosaurus, Triceratops, Tyrannosaurus, and Hadrosaurs and found that only one family namely the Hadrosaurs, or 'duck-billed dinosaurs' had evidence of cancer. Rothschild and colleagues found 29 tumors in bones of 97 members this group. Rothschild suggested that the food habits of these dinosaurs may have made them prone to cancer. Hadrosaurs ate conifers, which are high in carcinogenic chemicals. Identified tumors in this group included osteoblastoma, desmoplastic fibroma and metastatic cancer, however metastatic cancer was extremely rare and was found only in one specimen¹.

3000 BC to 1500 BC

Remains of the human mummies in Egypt provide the earliest evidence of human cancer. About 2250 years ago, some where in Egypt, a man today known only as M1, aged in his 50s struggled with a long, painful, progressive prostate cancer. He must have suffered from throbbing pain in his lower back, which then may have spread to other parts of his body and ultimately may have succumbed to his disease. Detailed analysis of this male Ptolemaic Egyptian mummy, from the Museu Nacional de Arqueologia (MNA) in Lisbon displayed several focal dense bone lesions located mainly on the spine, pelvis and proximal extremities. From the distribution of these osteoblastic metastatic lesions, it was hypothesized that prostate was the most likely origin of these metastatic lesions². A type of very aggressive bone cancer namely Osteosarcoma has also been observed in Egyptian Mummies. Bony destruction suggestive of head and neck cancer were observed in some Mummies.

It is obvious that cancer did not suddenly start appearing after modernization or industrialization. The oldest known description of human cancer is found in an Egyptian seven papyri, writing written between 3000-1500 BC. Two of them, known as the "Edwin Smith"³ and "George Ebers"⁴ papyri, contain details of conditions that are consistent with modern descriptions of cancer.

Edwin Smith Papyrus is assumed to be the oldest medical literature available. Written approximately in 3000 BC, Edwin Smith Papyrus contains 48 case reports that are written on a thin roll of papyrus 15 feet long. This contains description regarding 8 cases of tumors or ulcers of the breast. The writer concluded that bulging tumor of the breast was a grave disease with no significant curative options. The Edwin Smith Papyrus recommended cauterization (the fire drill) as a palliative measure.

The Ebers Papyrus dated 1500 BC, describes a soft-tissue tumor, a fatty tumor and recommends that this should be excised. However, if the tumor is large or livid and on a limb, the author recommends that this be left alone untouched. The Ebers Papyrus also contains descriptions suggestive of cancers of the skin, uterus, stomach, and rectum. Additional descriptions regarding enlarged thyroids, polyps were also available in the text. In addition to description of the medical conditions, the author also describes pharmacological, mechanical, and magical treatments for these disorders.

The Sumerians, Chinese, Indians, Persians, and Hebrews developed their own parallel systems and introduced herbal remedies such as tea, fruit juices, figs, and boiled cabbage as treatment for cancer. The ancient Egyptian system of treatment typically mixed medicine and religion. These physicians treated patients for several forms of cancer. Hieroglyphic inscriptions and papyri manuscripts suggest that these ancient physicians were able to distinguish between benign and malignant tumors. They suggested that the surface tumors may be removed surgically much similar to the current medical practice. Compounds of barley, pig's ear and other indigenous materials were suggested as treatment for cancer of the stomach and the uterus. Other commonly dispensed

medications included ointments, enemas, castor oil, suppositories, poultices and animal parts^{5, 6}. Most likely cancer was not a very prevalent disease in those olden days, because life expectancy was rather short and life style practices like prolonged breast feeding may have decreased the risk of breast cancer. It is worth noting that breast cancer is described more often than any other cancer in these ancient times.

Oldest specimens of cancer

The Kenam mandible is a jaw bone fragment found in Kenya by Louis Leakey in 1937. This is believed to be from an early hominid, estimated to have lived between 500,000 years to 1 million years ago. This specimen contained a tumor mass in the inner surface and this was often referred to the oldest specimen of cancer⁷. Some have suggested that this was osteogenic sarcoma, while others have argued that this could be Burkitt's lymphoma⁸. This mass was reexamined recently using latest techniques and the conclusion was that this was not a malignant tumor but instead was residue of a broken jaw⁹. The mummified skeletal remains of several Peruvian Incas, dating back 2400 years ago, contained abnormalities suggestive of malignant melanoma with diffuse metastases to bones, particularly of the skull and extremities.

Early years

Hippocrates, the great Greek physician (460-370 B.C), who is considered the father of medicine, is though to be the first person to clearly recognize difference between benign and malignant tumors. He is also the first person to use the terms cancer and carcinoma. Hippocrates noticed that blood vessels around a malignant tumor looked like the claws of crab. He named the disease Karakinos (the Greek name for crab) to describe tumors that may or may not progress to ulceration. His writings included description of cancers involving various parts of the human body. He used the word carcinos to describe a tumor, carcinoma to describe a malignant tumor and the word cancer to describe a non-healing malignant ulcer. Hippocrates has written extensively about diagnosis and medical treatment. His writing remained handwritten for centuries. In 1525 first Latin edition of Hippocrates writing appeared in print, and subsequently several Greek editions were published in Venice¹⁰. Hippocrates studied the natural history of various diseases and came to the conclusion that all diseases, including cancer, originate from natural

causes. Hippocrates believed that imbalance between four humors (blood, phlegm, yellow bile and black bile) was the causative factor for tumors. He proposed that the non-healing ulcerated cancers arose due to excess of black bile. Hippocrates has recognized the "dark, beef glaze like vaginal discharge" in association with uterine ulceration, cancers of the skin, mouth, breast, and stomach. Hippocrates has written about breast cancer and described this as a condition with bloody discharge and recognized that this may lead the condition of blood stained intra abdominal fluid. He described anorectal condylomas and polyps in his writing and recommended use of a speculum for rectal examination if the lesion was higher up in the colon^{11, 12, 13}.

Another renowned and influential Greek physician, Aulus Celsus (25 BC–AD 50) wrote, in Latin, his "De Medicina", an encyclopedic listing of medical advances to that date. Several centuries later his written notes were printed in a book form, which is often cited as the first printed medical book. Celsus continued the Hippocratic way of thinking comparing cancer to a crab. In his book he describes several varieties of superficial cancers of face, mouth, throat, and penis. He also describes cancers of deeper organs including stomach, colon, liver, and spleen^{13, 14, 15, 16, 17}. Celsus advocated treatment of superficial carcinomas with a topical application of boiled cabbage and a salted mixture of honey and egg white. He recommended that aggressive surgical treatment be undertaken for early cancer. He recognized that when breast cancer progresses, it tend to recur in the armpit which may lead to swelling of the arm, and in many cases may lead to death by spread to distant organs.

Claudius Galen (AD 129–217) is another great Greek physician who has given early description of cancer. He studied medicine at Alexandria and became one of the most famous physicians of ancient times. In Galen's text "De Tumoribus Praeter Naturam" he gives a detailed description of tumors. He also, like Hippocrates, believed that "humoral" changes in the body are responsible for the development of cancer. He believed that thick black bile caused ulcerated and incurable cancer, whereas thin yellow bile was responsible for non-ulcerated and curable cancer. Galen has recommended no treatment for cancer, unless the cancer was involving the skin, in which case surgery was the choice of treatment. Galen proposed that cancer was a disease of the sick and should be treated with purgatives to decrease the accumulation of black bile. He is credited with creation of the term sarcoma for tumors with the appearance of raw meat. Galen has

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written extensively on various topics. He has written more than 100 notes on tumors and cancers alone. Handwritten copies of his writing were very popular and were distributed to various countries around the world^{18, 19}.

Works of Hippocrates and Galen have been instrumental in releasing the practice of medicine from grips of superstitions and magic, and developing into a science of observation and logical reasoning. Aretaeus (AD 81-138) is credited with the first compilation of symptoms, signs and treatment of cancer of the uterus. He lived and practiced medicine in Alexandria, Egypt. He has recognized that there were two distinct forms of cancer: one was firm to the touch without ulceration and the other ulcerated and foul smelling. He wrote that both types of lesions as chronic and deadly, but the ulcerated lesions were especially bad with no hope of cure⁶.

Constantinople and history of cancer

In Europe the progress of medicine slowed down after the fall of the Roman Empire in AD 476. The great discoveries and revelations of Hippocrates and Galen spread to Constantinople and Bagdad, and these cities became prominent in the history of medicine.

Physicians of Constantinople continued to believe in the teachings of Hippocrates and Galen and developed the science further by their own observations. During this period, again, physicians continued to believe that cancer is caused by an excess of black bile, curable only in its earliest stages. At this time in history, intellectual headquarters of civilization spread across Constantinople, Cairo Alexandria and Athens. While this awakening was occurring in Constantinople, Europe was largely left in the darkness, where magic spells and myths ruled medical literature. Oribasius, a renowned physician, who lived Bagdad (325-403), had some interesting observations about cancer. He wrote that malignant tumors are painless most of the time. He also noted that malignant tumors were not as red as tumors arising from inflammation. He noted cutting of cancer tissue showed a scirrhous (firm) lesion mixed with coarse soft material (necrosis). Aetius (527-565), who was a royal physician in Constantinople, proposed mastectomy as a treatment of breast cancer²⁰. Teachings of Hippocrates and Galen were translated to Arabic by Rhazes of Bagdad (860-932). Rhazes had studied malignant tumors and suggested that surgeons

should not attempt to remove obstructions caused by cancer unless the cancer can be excised completely²¹. Albucasis (Spain: 1013-1106) is credited with introduction of surgical treatment of cancer²².

Renaissance period

In 1215, the Pope prohibited surgical operation asserting that this is a form of bloodshed. However, this did not stop some brave surgeons like Theodoric (1205-1296), who proposed that cancers, may invade muscle, blood vessels, and nerves. He proposed wide excision of cancer with healthy tissue around to ensure complete removal of the malignant tumor^{22, 23}. A renowned French surgeon, Guy de Chauliac (1300-1368), wrote a chapter about cancer in his book, *Chirurgia Magna*. He described cancers as cold (without signs of inflammation) lesions and advocated wide surgical excision as the treatment²⁴.

During the Renaissance, beginning in the 15th century, physicians acquired greater knowledge of the anatomy and physiology of the human body. This started an era, which has seen the advancement of surgery and development of rational therapies based on clinical observations. The theory that cancer is caused by excess of black bile continued to prevail through the 16th century. At this time cancer was considered incurable, however a variety of temporary measures were available including creams and pastes containing arsenic. Autopsies, performed by Harvey (1578-1657) in the 17th century, gave an insight in to the circulation system²⁵. By about the same period Gaspare Aselli (1581-1626) discovered the lymphatic system and this led to the demise of centuries old theory that excess of black bile causes cancer²⁶. The new theory suggested that abnormalities in the lymph and lymphatic system as the primary cause of cancer. A French physician, Claude Gendron suggested that cancer arises locally as a hard, growing mass, untreatable with drugs, and must be removed with all its "filaments"²⁷. The discovery of microscope and further experiments by Anthony Leeuwenhoek (1632-1723) added momentum to the quest for the cause of cancer.

Eighteenth century to modern era

In 1761, Giovanni Morgagni of Padua started the practice of doing autopsies to understand the relationship of patient's illness to pathologic findings after death. This practice greatly helped the progress of knowledge of medicine and oncology²⁸. Jean Astruc and chemist Bernard, two 18th century physicians conducted research to confirm or disprove then current theories related to the

origin of cancer. This was the pioneering efforts in experimental oncology. Many more physicians followed their footsteps, seeking better understanding of the secrets of cancer. John Hunter (1728-1793), a famous Scottish surgeon suggested that some cancers might be cured by surgery and described methods by which we can distinguish the surgically removable tumors. He suggested that, if tumor has not encroached to the nearby tissue and was still moveable, "There is no impropriety in removing it".

Discovery of anesthesia in 1844 by Wells allowed surgical techniques to flourish and the classic cancer operations such as radical mastectomy were developed²⁹. Three surgeons namely Billoth, Handley, and Halsted spearheaded "cancer operations" designed to remove the entire tumor along with the lymph nodes in the region where the tumor was located. The surgical work advanced so rapidly that the next hundred years became known as "the century of the surgeon." With progress of surgery, surgical resection of removable tumors became a routine practice. By late 19th century, with the development of better microscopes to study cancer tissues, scientists gained more knowledge about the cancer process. These studies showed that cancer cells are markedly different in appearance compared to the surrounding normal cells from which they originated. Rudolf Virchow, who is often called the founder of cellular pathology, provided the scientific basis for the modern pathological diagnosis of cancer. He described clinical course of cancer in relation with microscopic findings. This approach led to the development of modern cancer surgery. Tissues removed by the surgeons were examined under the microscope to make a precise diagnosis of cancer. By looking at the cut margin of surgical specimens the pathologist was able to tell the surgeon if the procedure had completely removed the tumor.

The early 20th century saw great progress in our understanding of microscopic structure and functioning of the living cells. Researchers pursued different theories to the origin of cancer, subjecting their hypotheses to systematic research and experimentation. A virus causing cancer in chickens was identified in 1911. Many chemical and physical agents that may lead to development of cancer were identified during later part of the 20th century. Later part of the 20th century also witnessed tremendous improvement in our understanding of the cellular

mechanisms related to cell growth and division. Many factors that suppress and activate the cell growth and division were identified and the knowledge continues to grow.

History of chemotherapy for cancer

Earliest documents indicate that various natural remedies were used for treatment of cancer. Medications including ointments, pastes, plasters, powders, aromatic water, wine and medicated herbal solutions were used in ancient times. Herbal products were the main ingredients of early cancer treatments, but minerals and animal products like liver, bone and urine were also used in treatment.

Pliny (AD 23-79) prescribed simple remedies (like cabbage juice) for the treatment of cancer. For oral use he developed a boiled mixture of ash of sea crabs, egg white, honey, and stinging nettle with salt³⁰. Celsus prescribed diet, medications and surgery for cancer. Galen proposed that cancer may be treated with compound natural herbal remedies¹⁵. Paulus of Aegina (625–690), an eminent Greek physician, proposed mandrake as a form of cancer treatment. Mandrake is a plant with split roots. It resembled the body and legs of a man and was believed to possess magical properties including ability to cure cancer³¹. Purgatives and paregoric remedies containing arsenic, camphor, licorice, honey, alcohol, and boiled viper's flesh were often used in Medieval Europe for the treatment of cancer and cancer related wasting¹³. Paracelsus (1493-1541), a physician from Switzerland introduced many chemicals including mercury, lead, sulfur, iron, zinc, copper, arsenic, iodine, and potassium for the treatment of various illnesses. He believed that gradually increasing doses of chemicals can be used as chemotherapy treatment for cancer³².

During later periods, various chemicals including mercury and arsenic were used as external and internal treatment for cancerous lesions. It was believed that use of iodine would help to prevent progression of breast cancer beyond the primary site^{33, 34}. Etmullerus in 1712 compiled a collection of available treatments for various illnesses and in this there are several references to treatment of cancer. In these descriptions of Tinctura vitriolata and crab's eye are mentioned as beneficial for treatment of cancer³⁵. Motherby's Medical Dictionary, published in 1791, recognized that cancer is incurable and recommended palliative treatment using vinegar, crow's foot, dogfennel, or arsenic³⁶. In and around 1850s belladonna plaster and mercurial soap gained prominence

as curative treatment of breast cancer^{37, 38}. The first clinical trial in the history of medicine was conducted in 1857 at Middlesex Hospital in London to compare the results of medical treatment to surgical treatment²³. The clinical trial ended without any clear cut conclusions to superiority of one modality of treatment over the other.

Ehrlich is credited with introduction of the term “chemotherapy”. In its early days the term was used for the practice of using chemicals like arsenic to treat syphilis. Ehrlich published a paper in 1891 describing staining methods to differentiate lymphoid and myeloid cells and first described the term myeloid leukemia³⁹. During this period Ehrlich was doing research hoping to develop chemotherapy drugs for cancer. He was working with various chemical compounds including paramidobenzol, phenylarsenoxyl, diamidoarsenobenzol, and pyocyanase for treatment of cancer. In 1909 Ehrlich summarized his own findings and cotemporary knowledge in a 247 page book, which is often referred to as the first book of chemotherapy for cancer⁴⁰. In 1896 Roentgen discovered X-ray and within the next few years radiation found its place in the treatment of cancer. It was later discovered that daily low doses of radiation spread over several weeks greatly improved the patient’s chance for a cure of cancer. This finding paved the path for development of modern radiation therapy, which is now far more complex in efficiency and precision. Development of radiation therapy, in addition to development of newer chemical compounds added further momentum to the cancer treatment.

Trysin and amylopsin were introduced in 1921, which is considered to be starting point of modern chemotherapy. Based on experiences in World War I and then an accident in World War II with mustard gas scientists concluded that this could be used as an anti-cancer agent. Examination of victims who died from exposure to Nitrogen mustard showed that many had atrophy of their bone marrow and lymph nodes. This observation lead to the introduction of Mustard gas in to the treatment of a group of hematological malignancies called lymphoma, or cancers of the lymph glands. Alfred

Gilman and Gustaf Lindskog used this drug in an animal model of lymphoma and found that it actually worked. This drug was first tried on a patient by name

Dr. Lindskog, who was having trouble breathing because of a large lymphoma tumor mass in his neck. The drug worked and the patient had a very dramatic response. Publication of this finding was delayed due to military secrets involved with Nitrogen mustard. Lindskog finally published his findings in 1946. Initially there was a real enthusiasm in the oncology field, however it soon gave away to despair and pessimism with the finding that the response to Nitrogen mustard is only short lived and incomplete. Many acclaimed physicians including famous hematologist William Dameshek, were so much disappointed by the apparent set back that they became harsh critics of national drug development program arguing that cancer could never be cured with drugs⁴¹.

Folic acid, a dietary component in the green leafy vegetables was soon identified as a necessary ingredient for normal bone marrow function. An observation that folic acid deficiency could produce bone marrow changes similar to exposure of Nitrogen mustard lead to interest in development of folic acid antagonists for the treatment of cancer. Initial folic acid antagonists were aminopterin and amethopterin. Sidney Farber of Boston found out that children with leukemia can be put in to temporary remission by folic acid antagonist aminopterin⁴². Amethopterin, now better known as methotrexate found many uses in the treatment of hematological malignancies and solid tumors. 1950s can be considered as the new era of chemotherapy and during this period many new drugs including pyrimidine antagonists, vinca alkaloids and actinomycin-D were introduced into cancer treatment^{43, 44}. The year 1956 brought a breakthrough with the announcement of cure of a patient with metastatic choriocarcinoma using the chemotherapy drug methotrexate, the first metastatic cancer cured to that date⁴⁵. Around 1951 Hitchings and Elion identified two drugs namely 6-thioquanine and 6-mercaptopurine which later became very important in the treatment of acute leukemia^{46, 47}.

Next several years witnessed the surge of newer and newer chemotherapy drugs for treatment of various hematological malignancies and solid tumors. Most prominent of these chemotherapy drugs were Fluorouracil, Doxorubicin, and Cisplatin.

Success in cure of choriocarcinoma was soon followed by reports of cure of Hodgkin lymphoma and childhood acute lymphoblastic leukemia in 1960s. Even with the discovery of some chemotherapy drugs, surgery and

radiation therapy were the main forms of treatment till mid 1960s. It was soon realized surgery and radiation cured only a fraction of patients. Chemotherapy was subsequently explored for adjuvant use, which is treatment of patients who had no gross disease after surgery or radiation, to prevent microscopic disease from progressing in future. Around this time various combination chemotherapies were developed and these combinations were found to be much more effective than use of single agent chemotherapy drugs. Conquest of metastatic testicular cancer was first reported in 1970s⁴⁸.

The age of targeted therapy began somewhere in 1990s. The first targeted monoclonal antibodies, rituximab (Rituxan) and trastuzumab (Herceptin) were used in the treatment of lymphoma and breast cancer respectively. An astonishing array of monoclonal antibodies is now in use and many more are in development. Around the same time several more classes of targeted therapy were introduced. This included Growth signal inhibitors like imatinib (Gleevec), Angiogenesis inhibitors like bevacizumab (Avastin), and antibody drug conjugates. Angiogenesis inhibitors targets new blood vessel

formation by the tumor. Antibody drug conjugates like Gemtuzumab ozogamicin (Mylotarg) consist of a monoclonal antibody bound to a highly potent chemotherapy drug. The antibody part targets the cancer cell and subsequently the molecule enters the cell and delivers the entire chemotherapy payload inside the cancer cell leading to the death of the cancer cell.

In the modern era most cancers are curable if identified in the early stages with combinations of surgery, chemotherapy and radiation. Many diseases are curable with chemotherapy and radiation even if they are metastatic or are in advanced in stage. List of diseases that can be cured even in advanced stage IV disease includes choriocarcinoma and other embryonal germ cell tumors of women, testicular cancer, Acute leukemia, Hodgkin's lymphoma, and some subsets of Non-Hodgkin's lymphoma, head and neck cancer and colon cancer. Treatment of cancer is a continuous and ongoing struggle between man and nature. With the advent of newer and newer treatments, the cancer retreats but find new mutations to defeat the new drug. In this battle cancer is losing more and more grounds and ultimately this is a battle, we human beings are going to win.

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