HISTORY OF CANCER

WHAT IS CANCER?

Cancer is a group of many related diseases. All forms of cancer involve out-of-control growth and spread of abnormal cells.

Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide more rapidly until the person becomes an adult. After that, normal cells of most tissues divide only to replace worn-out or dying cells and to repair injuries.

Cancer cells, however, continue to grow and divide, and can spread to other parts of the body. These cells accumulate and form *tumors* (lumps) that may compress, invade, and destroy normal tissue. If cells break away from such a tumor, they can travel through the bloodstream, or the lymph system to other areas of the body. There, they may settle and form "colony" tumors. In their new location, the cancer cells continue growing. The spread of a tumor to a new site is called *metastasis*. When cancer spreads, though, it is still named after the part of the body where it started. For example, if prostate cancer spreads to the bones, it is still prostate cancer, and if breast cancer spreads to the lungs it is still called breast cancer.

Leukemia, a form of cancer, does not usually form a tumor. Instead, these cancer cells involve the blood and blood-forming organs (bone marrow, lymphatic system, and spleen), and circulate through other tissues where they can accumulate.

It is important to realize that not all tumors are cancerous. *Benign* (noncancerous) tumors do not metastasize and, with very rare exceptions, are not life-threatening.

Cancer is classified by the part of the body in which it began, and by its appearance under a microscope. Different types of cancer vary in their rates of growth, patterns of spread, and responses to different types of treatment. That's why people with cancer need treatment that is aimed at their specific form of the disease.

In America, half of all men and one-third of all women will develop cancer during their lifetimes. Today, millions of people are living with cancer or have been cured of the disease. The risk of developing most types of cancer can be reduced by changes in a person's lifestyle, for example, by quitting smoking or eating a better diet. The sooner a cancer is found, and the sooner treatment begins, the better a patient's chances are of a cure.

Cancer is a disease that has created fear in patients and frustration in doctors for thousands of years. Today over half of all cancer patients are cured and the disease can be prevented in many others.

Oldest Descriptions of Cancer

Cancer has afflicted man throughout recorded history. It is no surprise that from the dawn of history doctors have written about cancer. Some of the earliest evidence of cancer is found among fossilized bone tumors, human mummies in ancient Egypt and ancient manuscripts. Bone remains of mummies have revealed growths suggestive of the bone tumor, osteosarcoma. In other cases bony skull destruction as seen in cancer of the head and neck has been found.

Our oldest description of cancer (although the term cancer was not used) was discovered in Egypt that dates back to approximately 1600 B.C. The Edwin Smith Papyrus, or writing, describes eight cases of tumors or ulcers of the breast that were treated by cauterization, with a tool called "the

fire drill." The writing says about the disease, "There is no treatment."

Origin of the Word "Cancer"

The origin of the word cancer is credited to the Greek physician Hippocrates (460-370 B.C.), considered the "Father of Medicine." Hippocrates used the terms "carcinos" and "carcinoma" to describe non-ulcer forming and ulcer-forming tumors. In Greek these words refer to a crab, most likely applied to the disease because the finger like spreading projections from a cancer called to mind the shape of a crab. Carcinoma is the most common type of cancer.

Renaissance Period

During the Renaissance beginning in the 15th century, scientists in Italy developed a greater understanding of the human body. Scientists such as Galileo and Newton began to use the scientific method, used today to study disease. Autopsies, performed by Harvey (1628) allowed an understanding of the circulation of blood through the heart and body that had remained a mystery.

In 1761, Giovanni Morgagni of Padua was the first to do something considered routine today. He performed autopsies to relate the patient's illness to the pathological findings after death. This laid the foundation for scientific oncology, the study of cancer.

The famous Scottish surgeon, John Hunter, (1728-1793) suggested that some cancers might be cured by surgery and described how the surgeon might decide which cancers to operate on. If the tumor had not invaded nearby tissue and was "moveable," he said, "There is no impropriety in removing it."

A century later the development of anesthesia allowed surgery to flourish and the classic cancer operations such as radical mastectomy were developed.

19th Century

The 19th Century saw the birth of scientific oncology with the discovery and use of the modern microscope. Rudolf Virchow, often called the founder of cellular pathology, provided the scientific basis for the modern pathological study of cancer. As Morgagni had correlated the autopsy findings observed with the unaided eye with the clinical course of illness, so Virchow correlated the microscopic pathology. This not only allowed a better understanding of the damage cancer had done to a patient, but also laid the foundation for the development of cancer surgery. Body tissues removed by the surgeon could now be examined and a precise diagnosis made. In addition the pathologist could tell the surgeon whether the operation had completely removed all the tumor.

Cancer Causes

From the earliest times, physicians have wondered about the cause of cancer. The Egyptians blamed cancers on the Gods.

Humoral Theory: Hippocrates believed that the body contained four *humors* (body fluids) - including blood, phlegm, yellow bile, and black bile. A balance of these fluids resulted in a state of health. Any excesses or deficiencies caused disease. An excess of black bile collecting in various body sites was thought to cause cancer. This theory of cancer was passed on by the Romans and was embraced by the influential doctor Galen’s medical teaching which remained the unchallenged standard through the Middle Ages for over 1300 years. During this period, the

study of the body, including autopsies, was prohibited for religious reasons, thus limiting knowledge.

Lymph Theory: Among theories that replaced the humoral theory of cancer was cancer's formation by another fluid, lymph. Life was felt to consist of continuous and appropriate movement of the fluid parts through solids. Of all the fluids, the most important were blood and lymph. Stahl and Hofman theorized that cancer was composed of fermenting and degenerating lymph varying in density, acidity, and alkalinity. The lymph theory gained rapid support. John Hunter (1723-1792) agreed that tumors grow from lymph constantly thrown out by the blood.

Blastema Theory: In 1838, German pathologist, Johannes Muller, demonstrated that cancer is made up of cells, and not lymph, but he was of the opinion that cancer cells did not arise from normal cells. Muller proposed that cancer cells arose from budding elements (blastema) between normal tissue. His student, Rudolph Virchow (1821-1902), the famous German pathologist, determined that all cells, including cancer cells, are derived from other cells.

Chronic Irritation: Virchow proposed that chronic irritation was the cause of cancer, but he falsely believed that cancers "spread like a liquid." It was shown by a German surgeon, Karl Thiersch, that cancers metastasize through the spread of malignant cells and not through some unidentified fluid.

Trauma: In spite of advances in the understanding of cancer, from the late 1800s until the 1920s, cancer was thought by some to be caused by trauma. This belief was maintained despite the failure to cause cancer in experimental animals by injury.

Parasite Theory: In the 17th and 18th centuries, cancer was by some felt to be contagious. In fact the first cancer hospital in France was forced to move from the city in 1779 because of the fear of the spread of cancer throughout the city.

A Nobel Prize was wrongly awarded in 1926 for scientific research documenting stomach cancer being caused by a certain worm. With the inability to confirm this research, scientists lost interest in the parasite theory.

Cancer Epidemiology

During the eighteenth century, three important observations were made that launched the field of cancer epidemiology.

- An Italian doctor, Bernardino Ramazzini, reported in 1713 the virtual absence of cervical cancer and relatively high incidence of breast cancer in nuns and wondered whether this was in some way related to their celibate lifestyle. This observation was an important step toward identifying and understanding the importance of hormonal factors such as pregnancy in modifying cancer risk.

- Percivall Pott of Saint Bartholomew's Hospital in London described in 1775 an occupational cancer in chimney sweeps, cancer of the scrotum, caused by soot collecting under their scrotum. This research led to many additional studies that identified a number of occupational carcinogenic exposures and led to public health measures to reduce cancer risk.

- John Hill of London was the first to recognize the dangers of tobacco. In 1761, only a few decades after tobacco became popular in London, he wrote a book entitled "Cautions Against the Immoderate Use of Snuff."

Cancer Treatments: Surgery

Ancient physicians and surgeons knew that cancer would usually come back after it was removed by surgery. The Roman physician Celsus wrote, "After excision, even when a scar has formed, none the less the disease has returned."

Galen was a second century Roman doctor whose books were preserved for centuries and who was thought to be the highest medical authority for over a thousand years. Galen viewed cancer much as Hippocrates had and his views set the pattern for cancer management for centuries. He considered the patient incurable after a diagnosis of cancer had been made.

Even though medicine progressed and flourished in some ancient civilizations, there was little progress in cancer treatment. The approach to cancer was Hippocratic (or Galenic) for the most part. To some extent this view that cancer cannot be cured has persisted even into the twentieth century. This has served to fuel the fear patients have of the disease. Some people, even today, consider all cancer incurable and delay consulting a doctor until it is too late.

Treatments for cancer went through a slow process of development. The Ancients recognized that there was no curative treatment once a cancer had spread; and intervention might be more harmful than no treatment at all. Galen did write about surgical cures for breast cancer if the tumor could be completely removed at an early stage. Surgery then was very primitive with many complications, including blood loss. It wasn't until the 19th and early 20th centuries that major advances were made in general surgery and specifically in cancer surgery.

There were great surgeons before the discovery of anesthesia. John Hunter, Astley Cooper, and John Warren achieved lasting acclaim for their swift and precise surgery. But when anesthesia became available in 1846, there emerged the great surgeons whose work so rapidly advanced the art that the next hundred years became known as "the century of the surgeon."

Three surgeons stand out because of their contributions to the art and science of cancer surgery: Bilroth in Germany, Handley in London, and Halsted at Johns Hopkins. Their work led to "cancer operations" designed to remove all the tumor together with the lymph nodes in the region where the tumor was located.

William Stewart Halsted, professor of surgery at Johns Hopkins University, developed the radical mastectomy during the last decade of the 19th century. His work was based in part on that of W. Sampson Handley, the London surgeon who believed that cancer spread outward by invasion from the original growth. Halsted did not believe that cancers usually spread through the bloodstream: "Although it undoubtedly occurs, I am not sure that I have observed from breast cancer, metastasis which seemed definitely to have been conveyed by way of the blood vessels." It was this belief that led surgeons to develop the radical cancer operation. This became the basis of cancer surgery for almost a century until it was replaced by the work of modern surgeons through clinical trials.

At the same time Halsted and Handley were developing their radical operations, another surgeon was asking, "What is it that decides which organs shall suffer in a case of disseminated cancer?" Stephen Paget, an English surgeon, concluded that cancer cells spread by way of the bloodstream to all organs of the body, but were able to grow only in a few organs. In a brilliant leap of logic he drew an analogy between cancer metastasis and seeds which "are carried in all directions, but they can only live and grow if they fall on congenial soil." Paget's conclusion that cells from a primary tumor spread through the bloodstream, but were able to grow only in certain, and not all, organs was an accurate and highly sophisticated hypothesis that was confirmed by the techniques of

modern cellular and molecular biology almost a hundred years later. This understanding of metastasis became a key element in recognizing the limitations of cancer surgery. It eventually allowed doctors to develop systemic treatments used after surgery to destroy cells that had spread throughout the body and to use less mutilating operations, for example, in treating many types of cancer.

Cancer Treatments: Hormone Therapy

Another nineteenth century discovery laid the groundwork for an important modern method to treat and prevent breast cancer. Thomas Beatson graduated from the University of Edinburgh in 1874 and developed an interest in the relation of the ovaries to milk formation in the breasts, probably because he grew up near a large sheep farm in rural Scotland. In 1878 he discovered that the breasts of rabbits stopped producing milk after he removed the ovaries. He described his results to the Edinburgh Medico-Chirurgical Society in 1896: "This fact seemed to me of great interest, for it pointed to one organ holding control over the secretion of another and separate organ." Because the breast was "held in control" by the ovaries, he decided to test removal of the ovaries (oophorectomy) in advanced breast cancer. He found that oophorectomy often resulted in the improvement of breast cancer patients. He also suspected that "the ovaries may be the exciting cause of carcinoma" of the breast. He had discovered the stimulating effect of the female ovarian hormone (estrogen) on breast cancer, even before the hormone itself was discovered. His work provided a foundation for the modern use of hormone therapy such as tamoxifen for the treatment and prevention of breast cancer.

A half century after Beatson a urologist at the University of Chicago, Charles Huggins, reported dramatic regression of metastatic prostate cancer following removal of the testes. Later, drugs that blocked male hormone were found to be effective treatment for prostate cancer, and these drugs are now being studied to determine their role in prevention of prostate cancer.

Cancer Treatment: Radiation

As the nineteenth century was drawing to a close, in 1896 a remarkable lecture was presented by a German physics professor, Wilhelm Conrad Roentgen, entitled "Concerning a new kind of ray." Roentgen called it the "X-ray", "X" being the algebraic symbol for an unknown quantity. There was immediate worldwide excitement. Within months, systems were being devised to use X-rays for diagnosis, and within three years radiation was used in the treatment of cancer. In 1901 Roentgen received the first Nobel Prize awarded in physics. Radiation therapy began with radium and with relatively low voltage diagnostic machines. In France a major breakthrough took place when it was discovered that daily doses of radiation over several weeks would greatly improve therapeutic response. The methods and the machines for delivery of radiation therapy have steadily improved. Today, radiation is delivered with great precision in order to destroy malignant tumors while minimizing damage to adjacent normal tissue.

At the beginning of the 20th century, shortly after radiation began to be used for diagnosis and therapy, it was discovered that radiation could cause cancer as well as cure it. Many early radiologists used the skin of their arms to test the strength of radiation from their radiotherapy machines, looking for a dose that would produce a pink reaction (erythema) that looked like a sunburn. They called this the "erythema dose," and this was considered an estimate of the proper daily fraction of radiation. In retrospect, it is no surprise that many developed leukemia.

Modern Day Carcinogens

At about the same time, other causes of cancer were discovered. In 1911 Peyton Rous, at the Rockefeller Institute in New York, described a sarcoma in chickens caused by what later became

known as the Rous Sarcoma Virus. In 1915 cancer was induced in laboratory animals for the first time by a chemical, coal tar, applied to rabbit skin at Tokyo University. One hundred and fifty years had passed since the most destructive source of chemical carcinogens known to man, tobacco, was first identified in London by the astute clinician, John Hill. It was to be many years until tobacco was "rediscovered" as a carcinogen.

Today we recognize and avoid many specific substances that cause cancer: coal tars and their derivatives such as benzene, some hydrocarbons, aniline (a substance used to make dyes), asbestos and others. Radiation from a variety of sources, including the sun is known to lead to cancer. To assure the public's safety, the government has set occupational standards for many substances such a benzene, asbestos, hydrocarbons in the air, pesticides, radiation, etc.

Several viruses are now implicated in cancer: longstanding liver infection with the hepatitis virus can lead to cancer of the liver; a variety of Herpes virus, the Epstein Barr Virus, causes infectious mononucleosis and has been implicated in non-Hodgkin's lymphomas and nasopharyngeal cancer; the human immunodeficiency virus (HIV) is associated with an increased risk of developing several cancers, especially non-Hodgkin's lymphoma; and human papilloma viruses(HPV) have been linked to cancers of the cervix, vulva and penis. Many of these associations were recognized long before scientists understood the mechanism by which the cancer was produced.

Cancer Treatment: Chemotherapy

The century of the surgeon had begun with the discovery of anesthesia in 1846. Fifty years later, in 1896, Roentgen presented his famous paper on the X-ray. During World War I soldiers who were exposed to mustard gas were found to have severe bone marrow depression. The first anti-cancer chemical was developed by the U.S. Army in the course of a search for agents more effective than the mustard gas used in World War I. It was called nitrogen mustard and it proved to have remarkable activity against a cancer of the lymph nodes called lymphoma. This agent served as the model for a long series of similar, but more effective, agents (called "alkylating" agents) that killed rapidly proliferating cancer cells by damaging their DNA. Two years after the discovery of nitrogen mustard, a different kind of drug was discovered by Sidney Farber of Boston. Dr. Farber described an anti-vitamin, a drug that blocked a critical chemical reaction needed for DNA replication. This drug was aminopterin (the predecessor of methotrexate, a commonly used cancer treatment drug today). Since then, other researchers discovered drugs that blocked different functions involved in cell growth and replication. The era of chemotherapy had begun. The first cure of metastatic cancer was obtained in 1956 when methotrexate was used to treat a rare tumor called choriocarcinoma.

Twentieth Century Understanding of Cancer

By the middle of the twentieth century scientists had in their hands the instruments needed to begin solving the complex problems of chemistry and biology presented by cancer.

The exact chemical structure of DNA, the basic material in genes, was discovered by Watson and Crick who received the Nobel Prize for their work. DNA was found to contain the genetic code that gives orders to all human cells, and after learning how to translate this code, scientists were able to see how genes worked and how genes could be damaged by mutations (changes or mistakes in genes). These modern techniques of chemistry and biology answered many complex questions about cancer. Scientists already knew that cancer could be caused by chemicals, radiation, and viruses, and that sometimes cancer seemed to run in families. But, as our understanding of DNA and genes increased, it became apparent that it was the damage to DNA by chemicals and radiation, or introduction of new DNA sequences by viruses that often led to the development of cancer. It became possible to pinpoint the exact site of the damage to a specific

gene in the DNA. Further, scientists discovered that sometimes defective genes are inherited, and that sometimes these inherited genes are defective at the same points that chemicals exerted their effect. In other words, most carcinogens caused DNA damage (mutations), mutations led to abnormal groups of cells (called clones), mutant clones evolved to ever more malignant clones over time, and the cancer progressed by more and more genetic damage and mutations. Normal cells with damaged DNA die; cancer cells with damaged DNA do not. The very recent discovery of this critical difference answers many scientific questions that have troubled scientists for many years.

Today, the study of cancer biology has become a very complex science as, slowly, medical scientists are identifying the genes that are damaged by chemicals or radiation and the genes that, when inherited, can lead to cancer. The recent discovery of two genes that cause some breast cancers, BRCA1 and BRCA2, represents considerable promise because many individuals who have a higher probability of developing breast cancer can now be identified. Other genes have been discovered that are associated with some cancers that run in families such as cancers of the colon, rectum, kidney, ovary, esophagus, lymph nodes, skin melanoma, and pancreas. Familial cancer is not nearly as common as spontaneous cancer, causing less than 15% of all cancers, but it is important to understand these cancers because we may be able to identify persons at very high risk with continued research in genetics.

The approach to patient treatment has become more scientific with the introduction of clinical trials on a wide basis across the country. These clinical trials, which compare new treatments to standard treatments, offer patients the best treatment available and at the same time contribute to a better understanding of treatment benefits and risks. Clinical trials test theories about cancer learned in the basic science laboratory and also test ideas derived from the clinical observations on cancer patients. They are essential to continued progress.

Early in the twentieth century, the only curable cancers were those that were small and localized enough to be completely removed by surgical removal. Later, radiation was used after surgery to control small tumor growths that were not removed by the surgery. Finally, chemotherapy was added to destroy small tumor growths that had spread beyond the reach of the surgeon and radiotherapist. The use of chemotherapy after surgery to destroy the few remaining cells in the body is called "adjuvant" therapy. Adjuvant therapy was tested first in breast cancer and found to be effective. It was later used in other cancers such as colon cancer, cancer of the testis, and others.

A major discovery was the advantage of multiple chemotherapeutic agents (known as combination chemotherapy) over single agents. Some types of very fast-growing leukemias and lymphomas, tumors involving the cells of the bone marrow and lymph nodes, responded extremely well to combination chemotherapy and clinical trials led to gradual improvement of the drug combinations used. Many of these tumors can be cured today by appropriate combination chemotherapy.

Cancer Treatments: Biologic Therapy

Scientists’ understanding of the biology of cancer cells has led to the development of biological agents that mimic some of the natural signals that the body uses to regulate growth. This cancer treatment, called biological response modifier (BRM) therapy, biologic therapy, biotherapy, or immunotherapy, has proven effective for several cancers through the clinical trail process.

Some of these biologic agents, occurring naturally in the body, can now be produced in the laboratory. Examples are interferons, interleukins, and other cytokines. These agents are given to patients to imitate or influence the natural immune response agents either directly altering the

cancer cell growth and acting indirectly to help health cells control the cancer. One of the most exciting applications of biologic therapy has come from identification of certain tumor targets, called "antigens", and aiming an antibody at these targets. This was first used as a means of localizing tumors in the body for diagnosis and more recently has been used to attack cancer cells.

Summary

The growth in our knowledge of cancer biology and cancer treatment and prevention has been staggering in recent years. It is likely that scientists will learn more about cancer in the last decade of this century than has been learned in all the centuries preceding. This does not change the fact, however, that all scientific knowledge is based on the knowledge already acquired by the hard work and discovery of our predecessors.

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