



The History of Cancer

The study of cancer, called *oncology*, is the work of countless doctors and scientists around the world whose discoveries in anatomy, physiology, chemistry, epidemiology, and other related fields made oncology what it is today. Technological advances and the ever-increasing understanding of cancer make this field one of the most rapidly evolving areas of modern medicine.

What is cancer?

Cancer begins when cells in a part of the body start to grow out of control. There are many kinds of cancer, but they all start because of out-of-control growth of abnormal cells. To learn more about how cancer forms and grows, see our document called *What Is Cancer?*

Cancer is the second leading cause of death in the United States. About one-half of all men and one-third of all women in the US will develop cancer during their lifetimes. Today, millions of people are living with cancer or have had cancer.

Oldest descriptions of cancer

Human beings and other animals have had cancer throughout recorded history. So it's no surprise that from the dawn of history people 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. Growths suggestive of the bone cancer called osteosarcoma have been seen in mummies. Bony skull destruction as seen in cancer of the head and neck has been found, too.

Our oldest description of cancer (although the word cancer was not used) was discovered in Egypt and dates back to about 3000 BC. It is called the Edwin Smith Papyrus and is a copy of part of an ancient Egyptian textbook on trauma surgery. It describes 8 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 BC), who is considered the "Father of Medicine." Hippocrates used the terms *carcinus* 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. The Roman physician, Celsus (28-50 BC), later translated the Greek term into *cancer*, the Latin word for crab. Galen (130-200 AD), another Roman physician, used the

word *oncos* (Greek for swelling) to describe tumors. Although the crab analogy of Hippocrates and Celsus is still used to describe malignant tumors, Galen's term is now used as a part of the name for cancer specialists — oncologists.

Sixteenth to eighteenth centuries

During the Renaissance, beginning in the 15th century, scientists developed greater understanding of the human body. Scientists like Galileo and Newton began to use the scientific method, which later was used to study disease. Autopsies, done by Harvey (1628), led to an understanding of the circulation of blood through the heart and body that had until then been a mystery.

In 1761, Giovanni Morgagni of Padua was the first to do something which has become routine today — he did autopsies to relate the patient's illness to pathologic 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 classic cancer operations such as the radical mastectomy were developed.

Nineteenth century

The 19th century saw the birth of scientific oncology with use of the modern microscope in studying diseased tissues. Rudolf Virchow, often called the founder of cellular pathology, provided the scientific basis for the modern pathologic study of cancer. As Morgagni had linked autopsy findings seen with the unaided eye with the clinical course of illness, so Virchow correlated microscopic pathology to illness.

This method not only allowed a better understanding of the damage cancer had done, but also aided the development of cancer surgery. Body tissues removed by the surgeon could now be examined and a precise diagnosis could be made. The pathologist could also tell the surgeon whether the operation had completely removed the cancer.

Cancer causes: Theories throughout history

From the earliest times, physicians have puzzled over the causes of cancer. Ancient Egyptians blamed cancers on the gods.

Humoral theory

Hippocrates believed that the body had 4 *humors* (body fluids): blood, phlegm, yellow bile, and black bile. When the humors were balanced, a person was healthy. The belief was that too much or too little of any of the humors caused disease. An excess of black bile 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 1,300 years. During this period, the study of the body, including autopsies, was prohibited for religious reasons, which limited progress of medical knowledge.

Lymph theory

Among theories that replaced the humoral theory of cancer was the formation of cancer by another body fluid, lymph. Life was believed to consist of continuous and appropriate movement of the fluid parts of the body through the solid parts. Of all the fluids, the most important were blood and lymph. Stahl and Hoffman theorized that cancer was composed of fermenting and degenerating lymph, varying in density, acidity, and alkalinity. The lymph theory gained rapid support. John Hunter, the Scottish surgeon from the 1700s, 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 believed that cancer cells did not come from normal cells. Muller proposed that cancer cells developed from budding elements (blastema) between normal tissues. His student, Rudolph Virchow (1821–1902), the famous German pathologist, determined that all cells, including cancer cells, are derived from other cells.

Chronic irritation theory

Virchow proposed that chronic irritation was the cause of cancer, but he believed incorrectly that cancers “spread like a liquid.” In the 1860s, German surgeon, Karl Thiersch, showed that cancers metastasize through the spread of malignant cells and not through some unidentified fluid.

Trauma theory

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

Infectious disease theory

Zacutus Lusitani (1575–1642) and Nicholas Tulp (1593–1674), 2 doctors in Holland, concluded at almost the same time that cancer was contagious. They made this conclusion based on their experiences with breast cancer in members of the same household. Lusitani and Tulp publicized the contagion theory in 1649 and 1652, respectively. They proposed that cancer patients should be isolated, preferably outside of cities and towns, in order to prevent the spread of cancer.

Throughout the 17th and 18th centuries, some believed that cancer was contagious. In fact, the first cancer hospital in France was forced to move from the city in 1779 because people feared cancer would spread throughout the city. Although human cancer, itself, is not contagious, we now know that certain viruses, bacteria, and parasites can increase a person’s risk of developing cancer.

Cancer epidemiology

During the 18th century, 3 important observations launched the field of cancer epidemiology (epidemiology is the study of causes, distribution, and control of diseases):

- In 1713, Bernardino Ramazzini, an Italian doctor, reported the virtual absence of cervical cancer and relatively high incidence of breast cancer in nuns and wondered if this was in some way related to their celibate lifestyle. This observation was an important step toward identifying and understanding the importance of hormones (like the changes that come with pregnancy) and sexually-transmitted infections and cancer risk.
- In 1775, Percival Pott of Saint Bartholomew's Hospital in London described an occupational cancer in chimney sweeps, cancer of the scrotum, which was caused by soot collecting in the skin folds of the scrotum. This research led to many more studies that identified a number of occupational carcinogenic exposures and led to public health measures to reduce a person's cancer risk at work.
- Thomas Venner of London was one of the first to warn about tobacco dangers in his *Via Recta*, published in London in 1620. He wrote that "immoderate use of tobacco hurts the brain and the eye and induces trembling of the limbs and the heart." And 150 years later, in 1761, only a few decades after recreational tobacco became popular in London, John Hill wrote a book entitled *Cautions Against the Immoderate Use of Snuff*. These first observations linking tobacco and cancer led to epidemiologic research many years later (in the 1950s and early 1960s) which showed that smoking causes lung cancer and led to the US Surgeon General's 1964 report *Smoking and Health*.

Epidemiologists continue to search for factors that cause cancer (like tobacco use, obesity, ultraviolet radiation), as well as those things that can help protect against cancer (such as physical activity and a healthy diet). This research provides evidence to guide public health recommendations and regulations.

As molecular biologists learn more about how factors cause or prevent cancer, this information is used to study molecular epidemiology, which is the study of interactions between genes and external factors.

Modern knowledge and cancer causes

Viral and chemical carcinogens

In 1915, Katsusaburo Yamagiwa and Koichi Ichikawa at Tokyo University, induced cancer in lab animals for the first time by applying coal tar to rabbit skin. More than 150 years had passed since clinician John Hill of London recognized tobacco as a *carcinogen* (a substance known or believed to cause cancer in humans). Many more years passed before tobacco was "rediscovered" as the most destructive source of chemical carcinogens known to man.

Today we recognize and avoid many specific substances that cause cancer: coal tars and their derivatives (like benzene), some hydrocarbons, aniline (a substance used to make dyes), asbestos, and many others. Ionizing radiation from a variety of sources, including the sun, is also known to cause cancer. To ensure the public's safety, the government has set safety standards for many

substances, including benzene, asbestos, hydrocarbons in the air, arsenic in drinking water, and radiation.

In 1911, Peyton Rous, at the Rockefeller Institute in New York, described a type of cancer (sarcoma) in chickens caused by what later became known as the Rous sarcoma virus. He was awarded the Nobel Prize for that work in 1968. Several viruses are now linked to cancer in humans, including:

- Long-standing infection with the hepatitis B or C viruses can lead to cancer of the liver.
- One of the herpes viruses, the Epstein-Barr virus, causes infectious mononucleosis and has been linked to non-Hodgkin lymphomas and nasopharyngeal cancer.
- People with human immunodeficiency virus (HIV) have greater increased risk of developing several cancers, especially Kaposi sarcoma and non-Hodgkin lymphoma.
- Human papilloma viruses (HPVs) have been linked to many cancers, especially those of the cervix, vulva, vagina, anus, and penis. Some head and neck cancers (mostly the tongue and tonsils) are linked to the high-risk types of HPV, too. Today there is a vaccine to help prevent HPV infection.

As of 2012, the World Health Organization's International Agency for Research on Cancer (IARC) has identified more than 100 chemical, physical, and biological carcinogens. Many of these associations were recognized long before scientists understood much about how cancer develops. Today, research is discovering new carcinogens, explaining how they cause cancer, and providing insight into ways to prevent cancer.

By the middle of the 20th century, scientists had the instruments they needed to work on some of the complex problems of chemistry and biology that remained unsolved. James Watson and Francis Crick, who received a Nobel Prize in 1962 for their work, had discovered the exact chemical structure of DNA, the basic material in genes.

DNA was found to be the basis of the genetic code that gives orders to all cells. After learning how to translate this code, scientists were able to understand how genes worked and how they 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 the understanding of DNA and genes increased, they learned that it was the damage to DNA by chemicals and radiation, or the 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 on a specific gene.

Scientists discovered that sometimes defective genes are inherited, and sometimes these inherited genes are defective at the same points that chemicals exert their effect. In other words, most of the things that caused cancer (carcinogens) caused genetic damage (mutations) that looked a lot like the mutations that could be inherited and could result in the same types of cancer if more mutations were introduced.

No matter which way the first mutation started (inborn or spontaneous), the cells that came from these mutations led to groups of abnormal cells (called clones, or duplicates of the abnormal cell). The mutant clones evolved to even more malignant clones over time, and the cancer progressed by more and more genetic damage and mutations. The big difference between normal tissues and

cancer is that normal cells with damaged DNA die; cancer cells with damaged DNA do not. The discovery of this critical difference answered many questions that had troubled scientists for many years.

Oncogenes and tumor suppressor genes

During the 1970s, scientists discovered 2 particularly important families of genes related to cancer: oncogenes and tumor suppressor genes.

Oncogenes: These genes cause cells to grow out of control and become cancer cells. They are formed by changes or mutations of certain normal genes of the cell called *proto-oncogenes*. Proto-oncogenes are the genes that normally control how often a cell divides and the degree to which it *differentiates* (or specializes in a specific function in the body).

Tumor suppressor genes: These are normal genes that slow down cell division, repair DNA errors, and tell cells when to die (a process known as *apoptosis* or *programmed cell death*). When tumor suppressor genes don't work properly, cells can grow out of control, which can lead to cancer.

It may be helpful to think of a cell as a car. For it to work properly, there need to be ways to control how fast it goes. A proto-oncogene normally functions in a way that is similar to a gas pedal — it helps the cell grow and divide. An oncogene could be compared to a gas pedal that is stuck down, which causes the cell to divide out of control. A tumor suppressor gene is like the brake pedal on a car. It normally keeps the cell from dividing too quickly just as a brake keeps a car from going too fast. When something goes wrong with the gene, which can happen if a mutation causes it to stop working, cell division can get out of control.

Slowly, medical scientists are identifying the oncogenes and tumor suppressor genes that are damaged by chemicals or radiation and those that, when inherited, can lead to cancer. For example, the 1990s discovery of 2 genes that cause some breast cancers, BRCA1 and BRCA2, is a step forward because these genes can be used to identify people who have a higher risk of developing breast cancer.

Other genes have been discovered that are linked to cancers that run in families, such as cancers of the colon, rectum, kidney, ovary, thyroid, pancreas, and skin melanoma. Familial cancer is not nearly as common as spontaneous cancer (cancer that is caused by DNA damage that starts during a person's lifetime). Cancer linked to heredity is less than 15% of all cancers. Still, it is important to understand these cancers because with continued research in genetics we may be able to identify more people at very high risk.

Once researchers recognized the importance of specific genetic changes in cancer, they soon began working to develop *targeted therapies* (drugs or substances that interfere with specific molecules) to overcome the effects of these changes in tumor suppressor genes and oncogenes.

Cancer screening and early detection

Screening refers to tests and exams used to find a disease, such as cancer, in people who do not have any symptoms. The first screening test to be widely used for cancer was the Pap test. The test was developed by George Papanicolaou as a research method in understanding the menstrual cycle. Papanicolaou soon recognized its potential for finding cervical cancer early and presented

his findings in 1923. At first, most doctors were skeptical, and it was not until the American Cancer Society (ACS) promoted the test during the early 1960s that this test became widely used. Since that time, the cervical cancer death rate in the United States has declined by about 70%.

Modern mammography methods were developed late in the 1960s and first officially recommended by the ACS in 1976.

Current American Cancer Society guidelines include methods for early detection of cancers of the cervix, breast, colon and rectum, endometrium, and prostate, as well as a cancer-related check-up which, depending on a person's age and gender, might include exams for cancers of the thyroid, mouth, skin, lymph nodes, testes, and ovaries.

Evolution of cancer treatments: Surgery

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

Galen was a 2nd-century Roman doctor whose books were preserved for centuries. He 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 the belief that cancer cannot be cured has persisted even into the 21st century. This has served to fuel the fear people have of the disease. Some people, even today, consider all cancer incurable and put off seeing a doctor until it is too late for optimal treatment.

Cancer treatment has gone through a slow process of development. The ancients recognized that there was no curative treatment once a cancer had spread, and that 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 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, the work advanced so rapidly 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: Bilioth in Germany, Handley in London, and Halsted in Baltimore. Their work led to "cancer operations" designed to remove the entire tumor along 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. (The general concept of the radical mastectomy can be traced all the way back

to Lorenz Heister, a German who wrote about his ideas for mastectomy and lumpectomy in his book, *Chirurgie*, published in 1719.)

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.” He believed that adequate local removal of the cancer would cure it — if the cancer later appeared elsewhere, it was a new process. That belief led him to develop the radical mastectomy for breast cancer. This became the basis of cancer surgery for almost a century. Then, in the 1970s, modern clinical trials demonstrated that less extensive surgery is equally effective for most women with breast cancer. Today, a radical mastectomy is almost never done and the “modified radical mastectomy” is performed less frequently than before. Most women with breast cancer now have the primary tumor removed (lumpectomy), and then have radiation therapy.

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 in 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 that “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 could 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 so that they could use less mutilating operations in treating many types of cancer. Today these systemic treatments may also be used before surgery.

During the final decades of the 20th century, surgeons developed greater technical expertise in minimizing the amounts of normal tissue removed during cancer operations. Like the trend from radical mastectomy to lumpectomy, progress was also made in removing bone and soft tissue tumors of the arms and legs without the need for amputation in most cases, and in avoiding a colostomy for most patients with rectal cancer. This progress depended not only on understanding cancer better as a disease and on better surgical instruments, but also on combining surgery with chemotherapy and/or radiation.

Until near the end of the 20th century, diagnosing cancer often required “exploratory surgery” to open the abdomen (belly) or chest so the surgeon could take tissue samples to be tested for cancer. Starting in the 1970s, progress in ultrasound (sonography), computed tomography (CT scans), magnetic resonance imaging (MRI scans), and positron emission tomography (PET scans) have replaced many exploratory operations. CT scans and ultrasound can also be used to guide biopsy needles into tumors.

Today, doctors use instruments with fiberoptic technology and miniature video cameras to look inside the body. Surgeons can operate using special surgical instruments through narrow tubes put into small cuts in the skin. These instruments can be used to look and work inside the abdomen (laparoscopic surgery) or chest (thorascopic surgery). A similar instrument, the endoscope, can be used to remove some tumors in the colon, esophagus, or bladder by entering through natural body openings such as the mouth or anus.

Less invasive ways of destroying tumors without removing them are being studied and/or used. Cryosurgery (also called cryotherapy or cryoablation) uses liquid nitrogen spray or a very cold probe to freeze and kill abnormal cells. Lasers can be used to cut through tissue (instead of using a scalpel) or to vaporize (burn and destroy) cancers of the cervix, larynx (voice box), liver, rectum, skin, and other organs. Radiofrequency ablation transmits radio waves to a small antenna placed in the tumor to kill cancer cells by heating them.

Evolution of cancer treatments: Hormone therapy

Another 19th 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. 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, Beatson decided to test removal of the ovaries (called oophorectomy) in advanced breast cancer. He found that oophorectomy often resulted in improvement for 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 and the aromatase inhibitors, to treat or prevent breast cancer.

A half century after Beatson’s discovery, Charles Huggins, a urologist at the University of Chicago, reported dramatic regression of metastatic prostate cancer after the testicles were removed. Later, drugs that blocked male hormones were found to be effective treatment for prostate cancer.

New classes of drugs (such as aromatase inhibitors, LHRH [luteinizing hormone-releasing hormone] analogs and inhibitors, and others) have greatly changed the way prostate and breast cancers are treated. Research to better understand how hormones influence cancer growth has guided progress in developing many new drugs for cancer treatment. It is also helping researchers look at new ways to use drugs to reduce the risk of developing breast and prostate cancer.

Evolution of cancer treatments: Radiation

In 1896 a German physics professor, Wilhelm Conrad Roentgen, presented a remarkable lecture entitled “Concerning a New Kind of Ray.” Roentgen called it the “X-ray”, with “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 3 years radiation was used in to treat 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 greatly improved the patient’s chance for a cure. The methods and the machines that deliver radiation therapy have

steadily improved since then. Today, radiation is delivered with great precision to destroy cancer tumors while limiting damage to nearby normal tissues.

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) which looked like sunburn. They called this the “erythema dose,” and this was considered an estimate of the proper daily fraction of radiation. It is no surprise that many of them developed leukemia from regularly exposing themselves to radiation.

Advances in radiation physics and computer technology during the last quarter of the 20th century made it possible to aim radiation more precisely. *Conformal radiation therapy (CRT)* uses CT images and special computers to very precisely map the location of a cancer in 3 dimensions. The patient is fitted with a plastic mold or cast to keep the body part still and in the same position for each treatment. The radiation beams are matched to the shape of the tumor and delivered to the tumor from several directions. *Intensity-modulated radiation therapy (IMRT)* is like CRT, but along with aiming photon beams from several directions, the intensity (strength) of the beams can be adjusted. This gives even more control over decreasing the radiation reaching normal tissue while delivering a high dose to the cancer.

A related technique, *conformal proton beam radiation therapy*, uses a similar approach to focusing radiation on the cancer. But instead of using x-rays, this technique uses proton beams. Protons are parts of atoms that cause little damage to tissues they pass through but are very effective in killing cells at the end of their path. This means that proton beam radiation can deliver more radiation to the cancer while possibly reducing damage to nearby normal tissues.

Stereotactic radiosurgery and *stereotactic radiation therapy* are terms that describe several techniques used to deliver a large, precise radiation dose to a small tumor. The term *surgery* may be confusing because no cut (incision) is actually made. The most common site treated with this radiation technique is the brain. The linear accelerator, or special machines such as the Gamma Knife or CyberKnife, can be used to deliver this treatment.

Intraoperative radiation therapy (IORT) is a form of treatment that delivers radiation at the time of surgery. The radiation can be given directly to the cancer or to the nearby tissues after the cancer has been removed. It is more commonly used in abdominal or pelvic cancers and in cancers that tend to recur (come back after treatment). IORT minimizes the amount of tissue that is exposed to radiation because normal tissues can be moved out of the way during surgery and shielded, allowing a higher dose of radiation to the cancer.

Chemical modifiers or *radiosensitizers* are substances that make cancer more sensitive to radiation. The goal of research into these types of substances is to develop agents that will make the tumor more sensitive without affecting normal tissues. Researchers are also looking for substances that may help protect normal cells from radiation.

Evolution of cancer treatments: Chemotherapy

During World War II, naval personnel who were exposed to mustard gas during military action were found to have toxic changes in the bone marrow cells that develop into blood cells. During that same period, the US Army was studying a number of chemicals related to mustard gas to develop more effective agents for war and also develop protective measures. In the course of that

work, a compound called *nitrogen mustard* was studied and found to work 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 growing cancer cells by damaging their DNA.

Not long after the discovery of nitrogen mustard, Sidney Farber of Boston demonstrated that aminopterin, a compound related to the vitamin folic acid, produced remissions in children with acute leukemia. Aminopterin blocked a critical chemical reaction needed for DNA replication. That drug was the predecessor of methotrexate, a cancer treatment drug used commonly today. Since then, other researchers discovered drugs that block different functions in cell growth and replication. The era of chemotherapy had begun.

Metastatic cancer was first cured in 1956 when methotrexate was used to treat a rare tumor called choriocarcinoma. Over the years, chemotherapy drugs (chemo) have successfully treated many people with cancer. Long-term remissions and even cures of many patients with Hodgkin disease and childhood ALL (acute lymphoblastic leukemia) with chemo were first reported during the 1960s. Cures of testicular cancer were seen during the next decade. Many other cancers can be controlled with chemo for long periods of time, even if they are not cured. Today, several approaches are being studied to improve the activity and reduce the side effects of chemo. These include:

- New drugs, new combinations of drugs, and new delivery techniques
- Novel approaches that target drugs more specifically at the cancer cells (such as liposomal therapy and monoclonal antibody therapy) to produce fewer side effects
- Drugs to reduce side effects, like colony-stimulating factors, chemoprotective agents (such as dexrazoxane and amifostine), and anti-emetics (to reduce nausea and vomiting)
- Agents that overcome multi-drug resistance (when the cancer doesn't respond to the usual treatment drugs)

Liposomal therapy is a technique that puts chemo drugs inside liposomes (synthetic fat globules). The liposome, or fatty coating, helps them penetrate the cancer cells more selectively and decreases possible side effects (like hair loss, nausea, and vomiting). Examples of liposomal drugs are Doxil (the encapsulated form of doxorubicin) and Daunoxome (the encapsulated form of daunorubicin).

Early in the 20th century, only cancers small and localized enough to be completely removed by surgery were curable. Later, radiation was used after surgery to control small tumor growths that were not surgically removed. Finally, chemotherapy was added to destroy small tumor growths that had spread beyond the reach of the surgeon and radiotherapist. Chemo used after surgery to destroy any remaining cancer 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 colon cancer, testicular cancer, and others.

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

The approach to patient treatment has become more scientific with the introduction of clinical trials on a wide basis throughout the world. These clinical trials compare new treatments to standard treatments and 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 drawn from the clinical observations on cancer patients. They are necessary for continued progress.

Evolution of cancer treatments: Immunotherapy

Better understanding of the biology of cancer cells has led to the development of biologic agents that mimic some of the natural signals that the body uses to control cell growth. Clinical trials have shown that this cancer treatment, called *biological response modifier (BRM) therapy*, *biologic therapy*, *biotherapy*, or *immunotherapy*, is effective for several cancers.

Some of these biologic agents, which occur naturally in the body, can now be made in the lab. Examples are interferons, interleukins, and other cytokines. These agents are given to patients to imitate or influence the natural immune response. They do this either by directly altering the cancer cell growth or by acting indirectly to help healthy cells control the cancer.

One of the most exciting applications of biologic therapy has come from identifying certain tumor targets, called antigens, and aiming an antibody at these targets. This method was first used to find tumors and diagnose cancer and more recently has been used to attack cancer cells. Using technology that was first developed during the 1970s, scientists can mass-produce monoclonal antibodies that are specifically targeted to chemical components of cancer cells. Refinements to these methods, using recombinant DNA technology, have improved the effectiveness and decreased the side effects of these treatments. The first therapeutic monoclonal antibodies, rituximab (Rituxan) and trastuzumab (Herceptin) were approved during the late 1990s to treat lymphoma and breast cancer, respectively. Monoclonal antibodies now are routinely used to treat certain cancers, and many more are being studied.

Scientists are also studying vaccines that boost the body's immune response to cancer cells. For instance, a 2009 lymphoma study looked at personalized vaccines made from tissue from each patient's tumor. Encouraging results showed that patients who received the vaccine lived longer disease-free than those who did not.

In 2010, the FDA approved Sipuleucel-T (Provenge), a cancer vaccine for metastatic hormone-refractory prostate cancer (prostate cancer that has spread and is no longer responding to hormone treatment). Unlike a preventive vaccine, which is given to prevent disease, Provenge boosts the body's immune system's ability to attack cancer cells in the body. This treatment has been shown to help certain men with prostate cancer live longer, though it does not cure the disease. It represents an important step forward in cancer treatment.

Evolution of cancer treatments: Targeted therapy

Until the late 1990s nearly all drugs used in cancer treatment (with the exception of hormone treatments) worked by killing cells that were in the process of replicating their DNA and dividing to form 2 new cells. These chemotherapy drugs also killed some normal cells but had a greater effect on cancer cells.

Targeted therapies work by influencing the processes that control growth, division, and spread of cancer cells, as well as the signals that cause cancer cells to die naturally (the way normal cells do when they are damaged or old). Targeted therapies work in several ways.

Growth signal inhibitors

Growth factors are hormone-like substances that help tell cells when to grow and divide. Their role in fetal growth and repair of injured tissue was first recognized in the 1960s. Later it was realized that abnormal forms of growth factors or abnormally high levels of growth factors contribute to the growth and spread of cancer cells. Researchers have also started to understand how cells recognize and respond to these factors, and how that can lead to signals inside the cells that cause the abnormal features found in cancer cells. Changes in these signal pathways have also been identified as a cause of the abnormal behavior of cancer cells.

During the 1980s, scientists found that many of the growth factors and other substances responsible for recognizing and responding to growth factor are actually products of oncogenes. Among the earliest targeted therapies that block growth signals are trastuzumab (Herceptin), gefitinib (Iressa), imatinib (Gleevec), and cetuximab (Erbix). Current research has shown great promise for these treatments in some of the more deadly and hard-to-treat forms of cancer, such as non-small cell lung cancer, advanced kidney cancer, and glioblastoma. And second-generation targeted therapies, like dasatinib (Sprycel) and nilotinib (Tasigna), have already been found to produce faster and stronger responses in certain types of cancer and were better tolerated.

Angiogenesis inhibitors

Angiogenesis is the creation of new blood vessels. The term comes from 2 Greek words: angio, meaning “blood vessel,” and genesis, meaning “beginning.” Normally, this is a healthy process. New blood vessels, for instance, help the body heal wounds and repair damaged tissues. But in a person with cancer, this same process creates new, very small blood vessels that give a tumor its own blood supply and allow it to grow.

Anti-angiogenesis agents are types of targeted therapy that use drugs or other substances to stop tumors from making the new blood vessels they need to keep growing. This concept was first proposed by Judah Folkman in the early 1970s, but it wasn't until 2004 that the first angiogenesis inhibitor, bevacizumab (Avastin), was approved. Currently used to treat advanced colorectal, kidney, and lung cancers, bevacizumab is being studied as treatment for many other types of cancer, too. And many new drugs that block angiogenesis have become available since 2004.

Apoptosis-inducing drugs

Apoptosis is a natural process through which cells with DNA too damaged to repair – such as cancer cells – can be forced to die. Many anti-cancer treatments (including radiation and chemo) cause cell changes that eventually lead to apoptosis. But targeted drugs in this group are different, because they are aimed specifically at the cell substances that control cell survival and death.

Cancer survivorship

Only a few decades ago, the prognosis (outlook) for people facing cancer was not nearly as favorable as it is today. During the 1970s, about 1 of 2 people diagnosed with cancer survived at

least 5 years. Now, more than 2 of 3 survive that long. Today there are more than 11 million cancer survivors in the United States alone.

Now that more people are surviving cancer, more attention than ever is focused on the quality of life and long-term outcomes of cancer survivors. Behavioral researchers are working to learn more about the problems survivors face. Some of these problems are medical, such as permanent side effects of treatment, the possibility of second cancers caused by treatment, and the need for long-term treatment and medical follow-up. Other problems are emotional or social challenges, like getting health insurance, discrimination by employers, relationship changes that may result from life-threatening illness, or learning to live with the possibility of cancer coming back.

Cancer was once a word that people were afraid to speak in public, and people rarely admitted to being a cancer survivor. Now, many celebrities and national leaders very openly discuss and share their cancer experiences. The view that cancer cannot be cured and the fears that have historically been attached to the disease are slowly changing.

The twenty-first century

The growth in our knowledge of cancer biology has led to remarkable progress in cancer prevention, early detection, and treatment. Scientists have learned more about cancer in the last 2 decades than had 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 – and we know that there is still a lot more to learn.

Cancer research is advancing on so many fronts that it's hard to choose the ones to highlight here.

More targeted therapies: As more is learned about the molecular biology of cancer, researchers will have more targets for their new drugs. Along with more monoclonal antibodies and small signaling pathway inhibitors, researchers are developing new classes of molecules such as antisense oligodeoxynucleotides and small interfering RNA (siRNA).

An example of this is a new class of targeted therapies called PARP inhibitors. (PARP is short for poly (ADP-ribose) polymerase enzymes.) Cancer cells use PARP to repair DNA damage, including the damage caused by cancer treatment. Recent studies in breast cancer have shown that blocking PARP can make cancer cells more sensitive to treatment and promote cell death.

BRAF is another gene that can produce a mutant cancer protein seen in about half of all melanomas. The drug vemurafenib (Zelboraf) targets this mutation. This drug prolonged overall survival in patients with inoperable melanoma compared to the standard drug dacarbazine. Vemurafenib was FDA approved in August 2011 for patients who have melanoma with this gene mutation.

Nanotechnology: New technology for producing materials that form extremely tiny particles is leading to very promising imaging tests that can more accurately show the location of tumors. It also is aiding the development of new ways to deliver drugs more specifically and effectively to cancer cells.

Robotic surgery: This term refers to manipulation of surgical instruments remotely by robot arms and other devices controlled by a surgeon. Robotic systems have been used for several types of cancer surgery; radical prostatectomy is among the most common uses in surgical oncology. As

mechanical and computer technology improve, some researchers expect future systems will be able to remove tumors more completely and with less surgical trauma.

Expression profiling and proteomics: Expression profiling lets scientists determine relative output of hundreds or even thousands of molecules (including the proteins made by RNA, DNA, or even a cell or tissue) at one time. Knowing what proteins are present in cells can tell scientists a lot about how the cell is behaving. In cancer, it can help distinguish more aggressive cancers from less aggressive ones, and can often help predict which drugs the tumor is likely to respond to.

Proteomic methods are also being tested for cancer screening. For most types of cancer, measuring the amount of one protein in the blood is not very good at finding early cancers. But researchers are hopeful that comparing the relative amounts of many proteins may be more useful, and that finding large amounts of certain proteins and less of others can provide accurate, useful information about cancer treatment and its outcomes. Proteins (and other types of molecules) are even found in exhaled breath, which is now being tested to find out if it can show early signs of lung cancer. This is an exciting area of research and early results in lung and colorectal cancer studies have been promising.

The American Cancer Society can help you learn more about cancer. Contact us anytime, day or night, for cancer-related information and support. Call us at **1-800-227-2345** or visit us online at www.cancer.org.

To learn more

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