A Look Back

From the time of Hippocrates, cancer was an incurable systemic disease caused by an imbalance in one of the bodily humors. Then, late in the Seventeenth Century at the dawn of the Enlightenment, the basic unit of life was discovered by the physicist Robert Hook while examining an onion skin through the eyepiece of an early microscope. What he saw was a geometric pattern the reminded him of the rooms that monks sleep in, so he called them cells.

Later in the Seventeenth century, French physician Francois de la Boe Sylvius wrote of his belief that in cancer, chemical changes in the body caused lymphatic fluids to change from “acrid to acid”.

Bernardino Ramazzini, an Italian physician, considered to be one of the founders of occupational medicine, observed in 1713 that nuns were more likely to get breast cancer and less likely to get cervical cancer than women who did not lead the religious life. He postulated that it was due to their lifestyle choice. Today we know that cervical cancer is caused by transmission of the human papilloma virus through sexual contact and that pregnancy confers some protection against breast cancer due to hormonal changes.

Hippocrates humoral theory of cancer was disproved by the French physician Jean Astruc. In 1769 he burned a slice of beef and a piece of cancerous breast tissue in an oven. Tasting both, and finding they tasted the same, he thus proved that tumor tissue did not have unusual levels of acid or bile.

English surgeon Percival Potts, after whom the Potts' fracture is named, showed that cancer can be caused by exposure to chemicals on the job. He noted that chimney sweeps in London – who were mostly young boys – suffered inordinately from scrotal cancer due to the accumulation of soot in their scrotal folds. That happened because they often performed their job while naked. Sweeps who wore a certain leather garment covering their genitals did not have an unusual incidence of the disease.

As the Eighteenth century progressed, physicians became more and more convinced that breast cancer was a localized disease. This change from Galen's belief in the systemic nature of cancer opened the door for surgery as a treatment.

The inventor of the stethoscope, Rene Theophile Hyacinthe Laemec, was the first to describe melanoma early in the

Nineteenth century. Noting that melanoma could spread to the lungs made him the first person to describe metastasis, Understanding that cancer can spread is an important to the understanding of cancer as a cellular disease.

The possibility that cancer is genetic in nature was first suggested by Dr. William Norris of Stourbridge, England in 1810. He described a family in which several generations suffered from the same type of cancer. This was taken farther by the French surgeon and anatomist Paul Broca who postulated that breast cancer might be heritable. Over several generations ten of the women in his wife's family died from the disease. Since chromosomes were unknown then, neither could have realized the significance of their observations.

While at the University of Wurzburg in 1858, Rudolph Virchow, a physician and civic reformer, published what he called "a pathology of the future." From his observations through the microscope, he formulated laws that describe how diseases develop in the body. Two of them are relevant to cancer. The first states that all cells come from the division of other cells. The second states that structural abnormalities of the flesh occur by "degeneration, transformations or repetitions of normal structures". That means that in 1858 science learned that cancer

is caused by malfunctioning healthy cells, not an imbalance of humors or any substance in the blood or lymph.

Surgery

The introduction of anesthesia in the 1840's and antisepsis in the 1860's enabled surgery to become the dominant treatment for cancer for the next one hundred years.

Austrian Theodor Bilroth, a pioneer of modern surgery, developed a number of "ectomies" as treatment for various cancers. He performed the first laryngectomy, the first successful stomach surgery, and the first bowel resection, all for the treatment of cancer. He was also the first to recognize the relationship between polyps and bowel cancer.

Many different surgeries were used to treat cancer during what is called the golden age of surgery. However, the procedure which seems to be the most significant and the most written about is the radical mastectomy for the treatment of breast cancer. Developed by William Halsted at Johns Hopkins in the 1890's, it was the standard treatment for breast cancer for nearly 100 years. Halsted knew that cancer was a cellular disease, but

at that time doctors did not know how cancer spread. Halsted worried that the operations he performed might actually be spreading the cancer he was trying to remove. So, to minimize the possibility of spreading the disease, he removed the tumor and a wide margin of tissue around it. As the surgery developed, more and more surrounding tissue was removed. In time, in addition to the breast, the underlying muscle and the lymph nodes in the armpit , under the clavicle and in the neck and chest were all removed. On source reported that early in the Twentieth century, surgery could include shoulder and hip amputation. Women who endured a radical mastectomy were “wounded and disfigured” for the rest of their lives. They suffered from ongoing pain and lymphedema as well as scarred and deformed bodies. It is easy to understand why some women chose not to have the surgery.

By the middle of the last century, science had proven that cancer spreads both through the lymphatic and circulatory systems. Surgery is not effective against this type of spreading and in 1976, Bernard Fisher, a pioneer in the biology and treatment of breast cancer, published findings showing that lumpectomy combined with chemotherapy or radiation is just as effective as radical mastectomy.

Today surgery remains a primary treatment for many cancers. It is now less invasive and greatly minimizes the removal of normal tissue. Laparoscopy, thorascopy and endoscopy are used to visualize and remove tumors. Lasers vaporize lesions of the cervix, larynx, liver, skin and rectum. Chyrosurgery freezes cancer cells and radio frequency ablation kills them with heat.

The German physicist Wilhelm Rontgen revealed in November of 1895 that he had discovered new and unknown electromagnetic rays that he called x-rays. By January of the next year, x-rays were being used to treat cancer. In the early years of radiation therapy, doctors did not know how radiation worked or its biological effects. Because of their lack of knowledge, physicians treating patients would often test the beam strength on their own arms to gauge what was thought to be the proper dose. That dose was called the “erythema dose” because it was the amount of radiation necessary to cause erythema which is a slight reddening of the skin that resembles sunburn. Many of the physicians who exposed their forearms in this way later died of leukemia.

Also in the early days, radiation therapy machines were limited in their effectiveness by their relatively low power. They were unable to treat deep tumors without causing excessive damage to

the skin and surrounding tissue. In the 1960’s, high energy megavoltage machines and linear accelerators produced high energy beams that could treat deep tumors with less damage to skin and surrounding tissues.

By the mid 1970’s and ‘80’s, advances in radiation physics and computer technology increased the precision of radiation treatment and the types of radiation treatments available. These therapies use CT scans or MRI’s and computers to pinpoint tumors in 3D and precisely hocus a beam of x-rays or protons on them while reducing the damage to surrounding tissues.

Abdominal and pelvic cancers are often treated during surgery. Because the tumor and the surrounding tissues are exposed, the radiation can be accurately delivered to the tumor while neighboring organs and tissues can be moved and shielded from radiation.

Research is also progressing in the search for new and better chemical modifiers and radio sensitizers. These are substances that make cancers more sensitive to radiation without affecting normal tissue. There is also research looking for compounds that could help protect normal cells from radiation.

Ultimately, radiation treatments are about delivering the right particle with the right energy to destroy cancer cells without harming surrounding tissues.

Peyton Rous

Early in the twentieth century, scientists were searching for a unifying theory of carcinogenesis. It was well known that substances such as radium, paraffin and soot can all cause cancer. The puzzle was how cancer could be caused by such different substances.

Around this time, Baltimorean Peyton Rous, who received his MD from Johns Hopkins in 1905, was the first to experiment with the molecular biology of Cancer. Working at what is now Rockefeller University, he investigated a sarcoma , a cancer of connective tissue, that developed spontaneously in Plymouth Rock hens. Trying to discover how the cancer spread from hen to hen, he injected tumor cells from one hen into others to see what might happen. What happened is that the inoculated hens developed the cancer. Then the question became; what caused the tumor? He filtered tumor cells through finer and finer filters and each time injected the filtrate into more hens. Each time the

inoculated hens developed the cancer. Finally, by filtering tumor cells through the finest filter then available, he was able to exclude any particle the size of a bacterium or larger. Injecting that filtrate into yet more Plymouth Rock hens; they too developed the sarcoma.

Rous concluded that the cause must be a “minute parasitic organism.” At that time, viruses, which were discovered in 1892, were the only biologically active particle having all the necessary properties. The virus he discovered was the first one shown to cause cancer; it’s called the Rous Sarcoma Virus or RSV.

And Rous was right, viruses are parasites; parasites that make more viruses to infect more cells by hijacking the host cell’s genetic mechanisms. But this process is not 100 percent perfect and viruses do sometimes acquire bits of DNA from their host cells. The section of DNA the Rous virus picked up directed the making of an entire protein. It is that protein that caused the sarcoma in the Plymouth Rock hens.

We now know that infections by a number of viruses can lead to cancer. Among them are:

Hepatitis B and C which are associated with liver cancer,

Epstein-Barr virus is associated with non-Hodgkin's lymphoma and naso- pharyngeal cancer,

HIV with Kaposi's sarcoma and Non-Hodgkin's lymphoma,

And the human papilloma virus is associated with cancer of the cervix, vulva, vagina, anus, penis, tongue and tonsil.

Hormone Therapy

During the 1890's, George Thomas Beatson – one time house surgeon to Joseph Lord Lister – was the first doctor to surgically remove ovaries to treat advanced breast cancer. He had found histological similarities between the breast tissue in lactating rabbits just after pregnancy and breast cancer. His insight was that substances released into the blood by one organ, the ovaries in this case, could influence another, the breast.

Fifty years later Canadian Charles Breton Huggins conducted research at the University of Chicago in which he was able to switch on prostate tumors in dogs by administering testosterone, which was isolated in 1935, and off by depriving them of it. After estrogen was purified in the 1940's, Huggins demonstrated

that estrogen and testosterone had the opposite effect on prostate cancer and that estrogen blocked the effect of testosterone. By treating prostate cancer with a chemical – estrogen - rather than surgically by castration, Huggins had shown that the systemic treatment of cancer was possible.

Huggins and Rous shared the Nobel Prize in Medicine or Physiology in 1966. Huggins received his recognition within a few years after his work was published. Rous, on the other hand, had to wait fifty years to receive his. The reason was technology. When Rous did his work, viruses were invisible to science. Proof of his discovery had to wait until technology, in this case the electron microscope, was invented and perfected enough to be widely available in research laboratories.

Chemotherapy

The possibility that drugs might be used to treat cancer did not begin to be taken seriously until the 1930's. But the real beginning didn't occur until after World War II with the declassification of events related to a bombing raid in 1943. While Allied freighters were anchored in the harbor at Bari, Italy, they were attacked by a flight of German bombers. One of the ships that were hit carried a load of nitrogen mustard which

had been used as the chemical warfare agent mustard gas; most notably in World War One, but not World War Two. Several hundred service men and civilians were exposed. Studies of the survivors showed a reduction in lymphocytes in their bone marrow and lymph nodes. After the war the use of the first chemotherapy drug, which was used to treat leukemia, and was derived from nitrogen mustards, grew rapidly in the United States. Unfortunately, there were only temporary and incomplete remissions.

Because of this and other failures, pessimism regarding chemotherapy was widespread during the 1950's. Despite spending millions of dollars on research, there was no evidence that drugs would benefit patients, much less cure them.

In the 1960's, the issue facing chemotherapy was whether the drugs used as chemotherapeutic agents did more harm than good. The prevailing mood continued to be pessimistic and many doctors felt that their patients were being poisoned for no reason.

The result was that cancer services were closed. One medical school would not allow its students an oncology clerkship/rotation. Physicians were fired or forced out of their jobs for testing new drugs, and the cancer service at the National Institutes of Health was referred to as "the butcher shop."

Proof that chemotherapy can cure cancer finally came with the cure of childhood acute leukemia and advanced Hodgkin's disease in adults. It had become clear to some researchers that combinations of drugs were more effective than administering just one agent. However, in the 1960's, administering multiple drugs was considered bad medical practice. The first such combination for treating childhood leukemia was called VAMP for the names of the drugs being given: vincristine, amethopterin, 6-mercaptopurine and prednisone. By the end of the decade remissions were up to 60%. One half of the remissions lasted years and were compatible with a cure. Today the aggressive use of combination chemotherapy programs cures most children with acute lymphocytic leukemia,

At the same time, Hodgkin's disease was almost always fatal. With single drug treatment, only 25% of patients had brief and incomplete remissions. Combination drug protocols called MOMP and MOPP were vigorously resisted and felt to be major departures from the norm. The results, however, were amazing. Remissions went from near 0% to 80%.

By 1970, chemotherapy was regarded as a cure for advanced Hodgkin's disease. This was the first time an advanced cancer of a major organ system in adults was cured by chemotherapy.

After 40 years about 60% of patients in the original MOPP study had not relapsed. Today, Hodgkin's disease in adults is about 90% curable.

From the 1970's through the 1990's thousands of drugs were randomly screened for effectiveness against various cancers. The problem was that when a promising drug was found, it could take decades to prove its effectiveness.

But modern Science has changed how drugs are screened. A deeper understanding of the molecular biology of cancer cells has replaced random screening with screening against specific molecular targets. The new therapies are called targeted therapies and work in several ways.

Enzyme inhibitors block proteins that cause cancer cells to grow. These therapies may not cure the disease, but they can slow tumor growth extending life and possibly allowing other forms of treatment time to work.

Apoptosis inducers target the mechanisms that cause cancer cells to die.

And angiogenesis inhibitors help restrict blood supply to tumors.

Targeted therapies are used to treat various types of breast cancer, colorectal, cancer, head and neck, kidney, lung and pancreatic cancers and are a major object of research.

More recently, the pursuit of individualized cancer treatments has focused targeted therapies on the unique mutations found in individual patients' tumors. This is because the genetic profiles of the tumors of two patients with the same type of tumor are not necessarily identical. The National Institutes of Health is working in concert with scientists around the world to publish on line and with open access The Cancer Genome Atlas. The Atlas is a listing of the complete genome of two hundred types of cancer and their sub types. The goal is to help predict the efficacy of cancer treatments for specific tumors in individual patients by discovering the mutations which are the most important in driving the patient's cancer.

One of the difficulties in designing and using genetic based treatments is that a tumor's genetic code changes as time passes. Additionally, tumors can have hundreds or thousands of changes in their genetic code. But only a few are likely to cause cancer. As a result, it is important to know which mutations to target for treatment.

Also, with so many possible variations, any new treatment may be effective for only a small number of people. And it's difficult to imagine a drug company being eager to spend millions of dollars to develop drugs for such a limited market. The answer may be to step back a bit from mutation by mutation treatments and to search for classes of mutations that function in the same or similar ways and to devise treatments that are effective against an entire class of mutations.

Research in this area is progressing rapidly. Almost every day we read something in the newspaper or online about an experimental treatment that saved a child with leukemia from death just as time was running out. Or we may see a report on the news about how data mining is enabling scientists to have a deeper understanding of what treatments may be best suited for a cancer with a particular genetic code.

Cancer Microbiology

The late Nineteenth and early Twentieth centuries were a time of great progress for cancer research and treatment. However, the fact that cancer is caused by genetic mutations would not become clear until the middle of the Twentieth century.

In the 1940's, Canadian Oswald Avery demonstrated that genes and chromosomes were made of DNA. Then, in 1953, Watson (who received his PhD at IU) and Crick revealed the double helix of DNA.

Progressing further along the path pioneered by Peyton Rous, J Michael Bishop decided to study the retrovirus MC29 because MC29 causes carcinomas - cancers of epithelial tissue - in birds and carcinomas are the most common type of cancer in humans. Bishop showed that a gene from the virus called the MYC gene causes tumors in myeloid cells in bone marrow. Myeloid tissue is the source of red blood cells and many white blood cells. We now know that the MYC gene is the most frequently activated oncogene in human cancers.

In 1976, Bishop's lab showed that normal mammalian cells have a gene that corresponds to the tumor promoting gene – known as SRC – in the Rous virus. Bishop proved that the gene found in mammals was the normal version of the SRC gene and that it makes a normal cell regulating protein. Subsequent research has shown that all retroviral oncogenes were acquired from normal genes. The genes in viruses that cause cancer are mutated versions of normal genes picked up from human cells. In addition, the SRC gene has been found in many species including humans, fruit flies and worms. That is significant because it would not be in so many different and varied species if it was not critical to life and, also, it must have developed early in evolution and been retained with little change.

Oncogenes

Sometimes you will hear people use the term "cancer gene". There is no such thing as a cancer gene. There are only mutated versions of normal genes that have gone over to the dark side. They are called oncogenes. The normal, unmutated form of an oncogene is called a "proto-oncogene".

Oncogenes are mutated versions of genes essential to cell division, or mitosis if you remember junior high biology. The

standard analogy is that oncogenes are like the accelerator in a car. Depressing the accelerator causes a car to go faster. When a proto-oncogene becomes an oncogene it becomes an accelerator of cell proliferation.

But, cancer is not only caused by an unstoppable acceleration of cell division. Normal cell division also has brakes that signal the cell to stop dividing. These brakes are called tumor suppressors. When a tumor suppressor is activated, cell division stops. When a tumor suppressor is mutated and loses its function, cell division continues unabated.

Most cancers are caused by a combination of oncogenes and tumor suppressors. The current estimate is that there are about five hundred oncogenes and 100 tumor suppressors.

The first “native” human oncogene was found by Robert Weinberg and Channing Der at MIT. In the late 70’sBishop and Varmus had demonstrated that proto-

oncogenes exist in all normal cells. What had not been proven is that proto-oncogenes exist in cancer cells. That was because a mutated and activated oncogene had never been found in a human cancer cell.

But Weinberg and colleagues were not the only ones searching for a human oncogene. Three other groups were also racing to be the first to make the discovery. In 1982, Weinberg and two other research teams all published their discoveries within a short period of time. As sometimes happens in science, they all made the same discovery at about the same time and even isolated the same gene called “ras”. Ras got its name because it had been found six years earlier in rat sarcomas. The normal version of ras is, like SRC found in all normal human cells and like SRC is functionally different in cancer cells. Normal ras encodes a protein that is tightly controlled to turn on and off. In cancer cells, the mutated gene encodes for a protein that is always on producing a constant signal promoting cell proliferation.

Tumor Suppressor Genes

The opposite of an oncogene is a tumor suppressor gene. Oncogenes accelerate cell division by their presence and tumor suppressors fail to stop cell proliferation by their absence.

Two important examples of tumor suppressors are the retinoblastoma gene – RB1, and one with the fancy name p53. When the RB1 gene is mutated and loses its ability to to halt cell division, children develop tumors of their eyes called retinoblastoma. There are two types of retinoblastoma, familial and sporadic. Children who inherit one mutated copy of RB1 and then acquire a mutation of their other copy have the familial variety and develop tumors in both eyes. In the sporadic form of the cancer, children are born with two normal copies of the gene, but develop mutations in both copies and have the disease in only one eye. However, RB1 is important not only because of retinoblastoma, but because the mutated gene is found in twenty to thirty percent of pancreatic, lung and breast cancers.

P53 has been known longer than RB1, but it took quite awhile to discover its function. In normal cells, p53's job is twofold. First it slows cell division in cells with damaged DNA so the cells have time to make repairs so as not to produce new cells with defective DNA. That's a good thing. But the best thing that can happen to a potentially cancerous cell is for it to die. P53's other job is to induce damaged cells to commit suicide. It does this by encouraging apoptosis.

Under normal circumstances, there is very little p53 in healthy cells because there is nothing that needs to be repaired or killed. But when cells suffer some trauma or stress that can damage their DNA, like a sunburn, tobacco smoke or whiskey, they go gangbusters producing p53 to repair or kill the damaged cells. Unfortunately though, p53 is like any defense tested beyond its limit, it fails. In our cells it becomes mutated and no longer protects us.

Research has shown that p53 is the most frequently mutated of all oncogenes and tumor suppressors. More than 6000 mutations have been found, and p53 activity is affected in more than 70 percent of human cancers. With so many mutations, the defective forms of p53 have come up with all kinds of ways to do harm. In addition to losing their tumor suppressor function, they can act like an oncogene and promote what they normally defend against; cell proliferation, cell survival, cell invasion and metastasis. For these reasons p53 is a major focus of cancer research.