Cancer: What is it?

W. Leigh Thompson, PhD, MD

Our bodies are made of billions of cells of hundreds of types. Some are formed early and remain unchanged throughout life. There is a nerve cell from your brain to your lower back that connects with another to your big toe. Adults don't make many new nerve cells, and cancers of such cells are uncommon. Liver cells are relatively long-lived, but if the liver is damaged, for example by hepatitis, the remaining liver cells "turn on" and grow new liver cells, but just enough to replace the injured cells. They don't grow two or three new livers. Cancers of such cells are more common. Some cells, like our blood, skin, and the linings of our gut, die quickly and are constantly replaced. Cancers of these cells are the most common.

A Boeing 747 airplane is much simpler but is also made of many different parts, each in just the right place and connected perfectly. Its instructions would fill a library, and an army of skilled specialists build and maintain it. If a part malfunctions it is replaced, but if one light is burned out they don't put back ten to replace it. That would be a tumor (from the Latin *swelling*). If the wing lights spread all over the wing and then took over the lavatories, they would have "metastasized" and it would be a cancer (from the crab-like invasion of normal structures).

Where is the blueprint of our body that keeps repairing it for a century? Why don't we have two noses or one eye? (A few people do have 12 fingers.) Instead of a library of blueprints we have just 35,000 instructions, our genes, and we got only one copy from each parent. These instructions are written with an alphabet of just four letters, the four nucleic acids (ACGT) that make up the DNA of all life on Earth.

We began when one of billions of sperm won the race to fertilize one of the third of a million eggs in our mother. If this tiny single cell, invisible to the naked eye, divided just 30 times, we would have 165 pounds of fertilized eggs–caviar. Instead, the instructions direct cells to bud off as limbs, to become eyes and kidneys, each at the right moment in the right place with the right shape.

Cancers begin when something changes these finely tuned instructions. Cells, even the ones that last 100 years, have "go" and "stop" signals that control when they will divide and form new cells and to stop such growth after just the right amount of repair. We are learning to stimulate even nerve cells to replace damaged nerves in adults, and "neuroimmunophyllins" may be able to re-grow the nerve cells in the "black stripe" in the brain whose death causes Parkinsonism. Cancers start when cells get too many "go" signals and not enough "stop" signals. Then any cell can begin to grow, divide, and make a small nest of cells. When this clump gets to be about 1/5 inch in diameter it needs new blood vessels to nourish it. With better blood supply it can continue to grow and cause local problems as it pushes normal cells to one side. If the lump is in your stomach or colon, it can grow very large before it causes mechanical problems, and it is usually detected because cancers and their new blood vessels tend to be fragile and bleed. If the tumor is in your brain, it doesn't have to be very big before it can cause paralysis, seizures and other major problems.

In addition to local swelling, some tumors begin to shed cells into the blood or lymphatic systems. Although millions of such cancer cells may have left home, only a few find a fertile place to nest and begin to grow as metastases. This is very important because one tumor in almost any location can be slashed or burned out, but once it spreads we have to poison it, and we are not very good at poisoning only the cancer cells. A new system under development detects a single cancer cell in 1/4 ounce of blood. In women with breast cancer, such a blood test detects a hidden cancer and predicts response to treatment. When drugs shrink the cancer, the cells in the blood decrease in number. If the cancer becomes resistant to the drugs, the first sign is an increase in these cells in blood. This may lead to a new way both to find and monitor treatment of many cancers.

We know that the genes of a cancer cell are different from normal because when it divides, each of the new cells continues to be the same kind of cancer. We used to recognize cancer because under the microscope the cells looked different from the normal cells surrounding them. Today we can either look for genes that indicate a cancer or, even more important, a tendency to form cancer. When a cancer is cut out, the surgeon removes some normal tissue around it and the pathologist examines that margin to be sure there are no cells that look like cancer. It is becoming possible to test the genes in the surrounding cells to tell if they will become cancer in the future, requiring a wider excision to be safe. Tests for genes are complex and timely, but many genes change the surface of the cell. We see textbook pictures of cells that look round and smooth, but cells actually look like a jungle of asparagus, broccoli and celery all mixed together. These projections from the cell surface are often antennae that detect the "go" signals that drive the cancer cells to divide. Sometimes one type of cancer has surface shrubbery that differs from normal, and we can make antibodies that bind only to such new foliage and thereby detect that cancer cell's garden. If that antibody is made fluorescent, we can see it on the surface of the cell. If we make a short strip of DNA fluorescent, it may bind to and signal presence of an altered cancer gene.

Some cancers make proteins that circulate in blood. A few cancers make normal hormones so there is an excess of adrenalin (causing rapid heartbeat, high blood pressure and sweating) or insulin (causing low blood sugar). Just as a pilot carries maps of every airfield in the world, each cell has the instructions for making all cells, including those that make hormones. So when a lung cell becomes cancerous it can lose its distinctive features and start making a hormone that normally comes from a gland in some other part of the body. This loss of the special features of the cell (dedifferentiation) is another characteristic of cancer.

Unfortunately, we haven't found enough such signal proteins in blood. We know that prostate-specific antigen (PSA) or the membrane-specific antigen (PMSA) are signals of most prostate cancers and also mirror the

cancer's response to treatment. Other signals are being found for other cancers.

Causes

Cancer begins with a change in the cell's instructions (genes) that causes too many "go" signals and not enough "stop" signals. Three kinds of injuries cause such gene damage.

The least common, but most feared, is energy that directly damages the delicate DNA structures of the genes and their control mechanisms. "Atomic" energy such as cosmic rays (you get more if you live in Denver at high altitude) or X-rays or radioactivity can do it, but our exposures are infrequent. The Japanese exposed to atomic blasts had increased cancers for decades, and Chernobyl has already caused more thyroid cancers in children. We fear this source because we don't control or understand it, but we are unlikely to be exposed and the best strategy is not to have excessive medical X-ray procedures. Sunlight and tanning parlors cause skin cancer, and these we can avoid.

Viruses cause cancer. Some viruses are composed mostly of DNA not unlike our genes. From infections of our ancestors, we carry in our genes many viral genes that may disrupt normal genes, resulting in cancer.

The DNA viruses that are most likely to cause cancer include hepatitis viruses, and both hepatitis B and C increase the risk of liver cancer. A herpes virus called Epstein–Barr, that causes mononucleosis, is associated with cancers of the nose and throat, cancers of the lymph cells that make antibodies (B-cell lymphomas), and an unusual lymphoma found in Africa and named for Sir Dennis Burkitt to whom we will return later.

One DNA virus, the human papilloma virus, causes many cases of cervical cancer. It is a sexually transmitted disease and when present greatly increases the risk of cervical cancer. There are new attempts to detect and treat the many strains of this virus, but a cheap low-tech device – the condom – prevents the infection.

The DNA of our genes stays in the nucleus of the cell, but the message is transcribed onto a similar molecule called RNA. RNA travels to the cytoplasm of the cell where it instructs small protein factories to assemble the right building blocks to make the proper protein coded by the gene.

Some viruses are made of RNA. When they infect us, they "reverse transcribe" DNA that then directs the infected cell to make many copies of the virus. One of these is the AIDS virus that specifically attaches to one piece of shrubbery on the surface of cells key to our immune defenses, thereby wrecking immunity. This virus is called the "human immunodeficiency virus," or HIV. In addition to the many other problems HIV causes, AIDS can be associated with unusual cancers. Condoms are multipotential – they also prevent AIDS.

Chemicals also cause gene damage that leads to cancer. Samuel Johnson's physician, Sir Percival Pott (1714–1788), was born on Threadneedle Street and became an outstanding surgeon of St. Bartholomew's Hospital after the surgeons split away from the barbers (their guild having been founded by Henry VIII). He treated chimney sweeps who undressed when they descended into the chimneys and who had a most unusual cancer: "The disease, in these people, seems to derive its origin from a lodgement of soot in the rugae of the scrotum." The same effect kills 430,000 Americans each year, 1000 times the deaths from combat in Iraq and more than 100 times the deaths in the 9/11 attack, although instead of rubbing against soot we actually inhale it and other poisons into our lungs!

Although some drugs cause cancer, such as the unusual young women's cancers associated with diethylstilbestrol (DES) use by their mothers, drugs have so many other bad effects that cancer may be the least of our worries. The trick is not to avoid all drugs, but to use them only when needed and to use them wisely.

Dietary chemicals also cause cancer. Alcohol does not itself cause cancer but increases the effects of tobacco. Fat in our diet and being fat increases cancer risks. Fiber is also important. Sir Dennis Burkitt decades ago showed slides of tiny hospitals in Africa and large hospitals in America and then showed slides of tiny stools in America and large, bulky, fiber-filled stools in Africa. He made his point! When humans had to collect grains and run down animals to eat them we were lean and mean and ate lots of fiber – we won the bridge run and didn't have colon cancer or heart attacks. Enough said. Maybe in 100,000 years we will evolve to be healthy couch potatoes.

We can also inherit cancer-causing genes. A normal gene on chromosome 13, Rb-1, protects us from having an eye cancer, retinoblastoma. If we don't have at least one of the usual pair of normal genes, we have a greater chance of having this rare tumor. Loss of another protective gene, WAGR, can cause other cancers in children.

Adding extra genes can interfere with normal cell control and cause cancer. If a piece of chromosome 9 becomes stuck on chromosome 22, called the "Philadelphia chromosome," it increases the risk of two forms of leukemia. Deletions of genes also cause cancer, and sometimes a piece of a chromosome is not properly duplicated and separated when a cell divides and one daughter cell is missing a critical set of genes and becomes cancerous.

Why do we have such errors in our genes without a radiation, virus or chemical cause? It is amazing we don't have more. Shakespeare wrote about 1,000,000 words in his life. Imagine having to copy 1,000 times this many words without a mistake! That is what each of your billions of cells does each time it divides. But it isn't perfect. Mistakes are common. In primitive life forms like viruses, these mistakes cause frequent changes. That is why the simple HIV virus is so deadly; we can't make a good vaccine because the virus changes so often through errors in its DNA replication. (It should go to Kinko's). Higher life forms have many proofreading mechanisms that find and repair DNA mistakes. Wasn't God clever when She designed us! Even so, we aren't perfect. The longer we live and the more times our cells divide, the more likely we will have errors that can cause cancer. Remember, in 1900 the average life span was 48 years and there were few cancers. Perhaps God didn't design us to survive so long and bankrupt Medicare.

Prevention and Treatment

Simple behavioral changes can prolong life: don't smoke, drink too much, or eat too much; wear condoms and seat belts; don't play with guns. These save you money as well as your life! Detecting cancers when they are still small and localized allows them to

be slashed or burned out. Simple inexpensive tests include mammograms and PAP-smears for women, blood tests for PSA and a rectal exam for men, and a test for unseen blood in your stool every six months with occasional colonoscopy. Your personal physician should help you do these. These are the big-bang, little-bucks preventions we can all do.

If you are at high risk, special screening may be appropriate. Some patients have polyps in their colons. Polyps can be tested to see if they have any of the three gene defects that together will cause colon cancer. If you have these genetic changes, or many polyps, you should have frequent screenings, or even prophylactic colectomy. If a woman has many relatives with breast cancer, she may have a defect in one of two protective genes called BRCA1 and BRCA2. These are seen in about 1% of women with breast cancer, but where there is a strong family history they are seen in about 8% and 3% of women with breast cancer.

BACH1 is a protein in the cell nucleus that reacts with the BRCA1 gene to repair breaks in the two strands of DNA that make up a normal chromosome. If BACH1 or BRCA1 is defective, such breaks are not repaired and can lead to cancer. Defects in these genes also increase the risk of cancer in the ovaries and Fallopian tubes.

If a woman has such a gene defect, especially with a strong family history, should she have prophylactic simple mastectomies and removal of tubes and ovaries? In 184 women who did not have the surgery 49% developed breast cancer, but that was the outcome in only 2% of 105 women who did have the prophylactic surgery and were followed for about 6.4 years. In 58 women with BRCA1 defects who had prophylactic removal of their tubes and ovaries, 9% were found to have previously undetected cancers in those organs but no new cancers thereafter.

Slash and burn. Surgeons and radiation oncologists are superb in their ability to cure localized cancers or to effectively treat metastases.

Poison. We also have many expert oncologists who know just the right combination and doses of poisons to cure or suppress many cancers. Even more extreme treatments are available, such as transplantation of bone marrow after intense chemotherapy wipes out both the tumor and the sensitive bone marrow cells. Although we have discussed "go" signals that cause cancer, such growth factors are also very valuable to stimulate formation of red or white blood cells that are damaged by intense chemotherapy.

Starve. Some cancers require continued stimulation from "go" signals to keep growing. If we can turn these off, it will both prevent and treat such cancers. Since Professor Charles Huggins in the 1940s we have known that certain tumors are stimulated by normal body hormones. Many breast cancers grow under stimulation by the normal female sex hormone, estrogen. That is why drugs that block estrogen, such as tamoxifen or Evista, are effective in treating and preventing such cancers. Many prostate cancers are stimulated by the normal male sex hormone, testosterone. A simple treatment is to remove the testes that form most of the testosterone, but alternatives include drugs that stop its formation or block its effects. Recently other growth factors, or their receptors on cancer cells that they stimulate, have been identified. Antibodies to these, such as HER-2 in breast or CD20 in white blood cell cancers, have been shown to slow or stop cancer growth.

Support. Sir William Osler reminded us: "We cannot cure all patients but we can care for all." If cancer is found, it is not hopeless. Many cancers can be cured. Most can be slowed, often for many years. But the quality of life of every patient can be improved. Pain can be treated. Other effects also can respond to simple treatments. Caring is essential. I am impressed that those physicians who choose to specialize in treating cancer are not only very technically advanced to bring the newest and best treatments to their patients, but they are also very caring.

Albert Owens, MD, one of the pioneers of modern oncology who built the huge cancer center at Johns Hopkins, is such a model of a caring oncologist who has taught two generations of others. He was the protegé of E. K. Marshall who was the second Chairman of Pharmacology and Experimental Therapeutics at Hopkins. Now in his 78th year, Dr. Owens heads a small group of Hopkins scientists that has found a key enzyme that may be a way to recognize many cancers early and to cure cancer, tuberculosis, and obesity – seemingly magic, but that has been the story of his career.

The Future. As we grow older, we will have more risk of cancer. That won't change. Early detection will find more curable early tumors or identify people at risk who don't even yet have a real cancer. This will be exciting if we can afford the tests and if we use them. But how many people today use proven methods such as condoms, testing for blood in your stools, and stopping smoking? As we study cancers not by their microscopic appearance but by the actual genes that are controlling these aberrant cells, we will have many new treatments, each of which will contribute to improved survival. But today we have many treatments that don't get to everyone in America, and cancer death rates are higher in poor neighborhoods and among Americans of minority racial origin. To paraphrase the proverb: A dollar of prevention is worth a C-note of cure.

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US Health Care: Triumph in Crisis

W. Leigh Thompson, Ph.D., MD

US health research, education, training, and technology is by far the best and attracts those who can to come here for care. When Senator Hillary Clinton proposed revolutionary changes in health care, her process was so inflammatory that a decade later no one wishes even to discuss comprehensive changes. Suggesting change is like hitting a wasps' nest with a stick–you soon find that everyone else has disparate vested interests and opposes all suggestions. I know that everything I will suggest is controversial; I just don't know any better solutions.

There are three reasons to consider change: cost, access, and quality.

Cost

In 1965 at the beginning of Medicare and Medicaid, the 194 million Americans generated an average GDP of $3700 each and spent 5.4% of it, $200, on health care. Today, the 294 million Americans generate an average GDP of $39,566 each and spend 16.5% of it, $6546, on health care. In an 80-year life span at today's spending that amounts to $524,000. Health care costs inflate the prices of American products, reducing their world markets and shifting US jobs to foreign workers.

Costs can be reduced by doing less, by doing it for less, or by doing it for fewer patients. One cause of health care inflation is the entitlement mentality of US citizens and politicians–that everyone deserves everything paid for by someone else. Congress mandated that health care for all patients with chronic renal disease be funded by Medicare, without providing the funds. Before that entitlement, hemodialysis was available for selected patients, but now 275,000 patients are being dialyzed whether or not they have Alzheimers or metastatic cancer. In the UK if you are old and have renal failure, you get a nice funeral. You have seen the advertisements for motorized wheelchairs or diabetes testing supplies for patients with Medicare. Entitlements are incremental; new ones don't replace and old ones never die.

Some care is cost effective. Drugs for tuberculosis and psychosis have emptied the sanitaria and mental hospitals. Drugs that block stomach acid have eliminated surgery for peptic ulcers. Antidepressants have increased worker productivity and quality of life. Some cancers are being cured. Entitlements don't select the most effective care within a fixed budget; once approved, everyone is eligible for a new intervention and the taxpayers get the bill.

Rationing is anathema, but we do it routinely with the scarcest and most valuable resources–human donor organs. Regions in the UK have a fixed government-funded budget for health and allocate resources according to local priorities. They choose how many neonatal ICU beds will treat babies weighing less than 1500 grams born to mothers abusing alcohol and cocaine vs. how many liver transplants for alcohol abusers who continue to drink vs. lung volume reduction surgery for patients with emphysema who continue to smoke, etc. Resources may not be available for some patients needing expensive but marginally effective care. Of course any UK resident can pay for any private care. (Senator Clinton's proposed US health care revolution would have made paying for health care a crime.)

The costs of malpractice extend far beyond the payments to insurers, lawyers, and patients. To protect themselves, physicians order every imaginable test and treatment so they won't be second-guessed. We need a total quality management approach to health care that minimizes and appropriately compensates for errors, but avoids lawyers and huge insurance premiums.

Access

Although 14% of Americans lack health insurance today, that does not mean they don't get needed care. It does mean that their care is probably less comprehensive, poorly organized, and less cost effective than it should be. Since you pay for much of this care, and for the costs of lack of good care, you should be concerned.

The federal government runs a large health care system for the uniformed services, merchant seamen, veterans, government employees and retirees, etc. It is in the forefront of implementation of electronic patient records and prescribing evidence-based treatments. It is the site of important research and training of health care professionals. Before 1965 these facilities were augmented by government-funded but locally-managed city hospitals. Bellevue, Boston City, Cook County, LA County, Charity, etc. had the best care, the best research, and the most sought-after training, yet they were highly cost-effective for uninsured patients. They were scrapped when all Americans became entitled to a private doctor and a private room. Perhaps care for the uninsured could be guaranteed in an expanded version of federal health care facilities that could recapture some of the qualities of the discarded city hospital system.

During the draft, all physicians served in the uniformed services. Today, eight years of undergraduate and medical education in a top university may cost $300,000 and new physicians aren't going to pay that off during their additional three to six years of specialty and subspecialty training. Why not make medical education free in return for perhaps two years of service, with the same requirement for licensing of foreign medical graduates? The additional 40,000+ physicians could care for all the uninsured, extend their own specialty training, enhance their skills, and provide the *pro bono* service that makes up a considerable part of the practice of many physicians. A similar strategy could be applied to the six-plus years of professional education of nurse practitioners and clinical pharmacists who are valued members of the health care team.

Quality

Robotic, fiberoptic, and micro-surgery are amazing. Dynamic MRI, CT, and PET scans provide precise anatomy, guide care, and detect problems early in their evolution. The technological quality of our health care is truly amazing.

Although we have by far the most expensive health care, the US ranks 37th in overall performance nationally and 72nd in population health. Canada

is 10th in spending and 30th and 35th in the other ratings (WHO whr2001). Why don't we get what we pay for?

The Institute of Medicine reports that more than 100,000 Americans die each year of preventable medical errors. Handwritten prescriptions are misinterpreted. Drug choices or doses are inappropriate. Multiple drugs interact but the prescribers are unaware the patient is taking other drugs. Tests are repeated because results are not provided to all the patient's practitioners. Patients arrive for emergency care but their handwritten chart can't be found. Such errors would be greatly reduced if medical records and prescriptions were electronic and shared with all the legitimate practitioners caring for the patient. The technology has been available for more than a decade. Physicians, however, have not embraced computer technology, some of which has not been user-seductive and time-saving. Recent privacy legislation complicates sharing of medical information. You may not want it widely known that you are HIV-positive, but should that concern prevent your gastroenterologist from knowing that your cardiologist has prescribed a drug that causes nausea, vomiting, and diarrhea?

Professor Ron Howard suggested decades ago that we have different levels of health care reimbursement. Everyone would have a silver plan that provides basic services, perhaps in a governmental institution as described above. You and your employer could purchase a gold plan which would reimburse for some or most, but not all, of cost-effectivecare in any facility. The premium for the gold plan might be reduced for patients who don't smoke, drink, or eat excessively; who wear seat belts and condoms; and who manage their blood pressure and blood sugar appropriately. For an additional premium you could also purchase a platinum plan which would reimburse most of nearly any care.

We could decide to fund more health care and less social security and defense, but we will lose jobs to foreign workers whose health care costs are far less than ours. If you believe in big government entitlements, then you must accept big government regulation of your health care. If you believe in free enterprise, there needs to be a marketplace to reward innovation and cost-effectiveness and the means to pay for it. If you believe in quality, you shouldn't stand for being killed by poor penmanship and miscommunication.

What scares me is there seems to be no national will to examine reforms and instant resistance to every suggestion, yet the spending grows, the uninsured fraction grows, and the quality deteriorates. I guess we don't care about the bridge getting rusty until our car goes in the river.

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