

Cancer Research in the 21st Century

Disclaimer: Dr. Woodgett is a research scientist at the Ontario Cancer Institute/Princess Margaret Hospital. This series of articles concern various aspects of cancer and efforts to develop new treatments. The information provided is not intended to provide medical advice nor provide opinion of appropriate treatment. Your physician is the best qualified individual to consult with questions about your health and well being.

One in three Canadians can expect to be afflicted with some form of cancer during their life-span. As our population ages, this incidence will increase because the probability of cancer increases with age. This year (2000) it is estimated that 132,100 new cases of cancer and 65,000 deaths from cancer will occur in Canada (<http://www.cancer.ca/stats2000/index.html>). Over the past 50 years, advances in cancer treatment and detection have been incremental. With a few notable exceptions (for example, childhood leukaemia), progress has been pedestrian and improvements largely confined to subtle changes in quality of life, dosages and patient education (a healthy diet and lifestyle playing a large role). How can this sobering scenario be reconciled with the seemingly daily announcements of breakthroughs in understanding human disease? In the last thirty years, there has been an incredible deluge of information about the genesis and progression of cancer, the mechanisms that go awry in pre-cancerous cells, the contributing risk factors and in the development of models. So why haven't there been commensurate drops in cure or incident rates? In this series of articles I will try to explain this "reality gap" as well as give examples of recent developments that are evidence that research is beginning to win the war against this disease.

1. What is cancer? A jargon-suppressed explanation of the devious genesis of cancer and why it's such a formidable challenge to deal with.
2. Breaking through the breakthrough hype. Why seemingly wondrous research discoveries never appear in the clinic. It's not a conspiracy, it's about how little we really know and the hurdles that have to be jumped to take a promising laboratory result and convert it into a treatment. On the brighter side, there are some very promising developments now reaching the clinic.
3. New technologies. How new technologies in computing, molecular biology, physics and robotics are reasons to believe our children will not fear cancer.
4. What can you do now? Tomorrow's technologies aren't much use today but there are many things you can do to reduce risks. Why early detection can make a huge difference.

Part 1. Know thy enemy

The first thing to remember is that cancer is not one disease but a collection. Pathologists with many years of training are able to classify over 150 different types of cancer by looking at properties such as the shape and colour and location of the tumour. They use specific stains to highlight cancer cells within normal tissue and many tricks to tell between similar types and stages of development. By classifying the tumour, a pathologist is able to gain predictive "prognostic" information which helps in assessing the type of treatment that is most likely to work. However, we know this information is incomplete. Each tumour only reveals a tiny fraction of its make-up. Two patients with apparently identical cancers, treated in the same way may have very different responses. Their tumours may have shared a few characteristics like the tip of two icebergs but under the surface have many hidden differences. In fact, no two tumours are ever exactly alike. This is because we are all unique individuals and cancers develop from our own cells. We differ at the genetic level (with different mothers and fathers) but more importantly for cancer, we differ in our experiences, our exposure to the environment, diet, sunlight, chemicals.

This is also a major reason for the difficulty in treating cancers. Our bodies have developed elaborate and clever defense systems that search out and kill foreign invaders. This immune response can even detect microbes and viruses hiding inside our cells. Every day, your immune system patrols every nook and cranny of your body, detecting invaders and eliminating them. However, cancer cells are largely invisible to this surveillance system because the cancer cells are wearing the same clothes as your normal cells. We know the immune system does detect some cancer cells because suppression of the immune system can lead to increased incidence of certain cancers. This is the basis for research into generating cancer vaccines. However, such vaccines are unlikely to protect against all types of cancer. This is because cancer cells continuously evolve. Since cancer cells are our cells and our bodies have difficulty distinguishing between them, perhaps it isn't surprising that drugs have a hard time too.

To understand the genesis of cancer, we have to remember that our bodies are made up of billions of cells. Each cell, be it within your kidney, heart, brain, skin, contains two complete copies of DNA which is spindled into large clumps called chromosomes. You inherit one complete set of 23 chromosomes from each parent. DNA is the blueprint of life and contains the complete set of instructions (the genes) for making between 50-100,000 different types of proteins (we still don't know the real number yet). Since you have two copies of human DNA, you have two copies of every gene. If one gene is inactivated, the other can usually take its place (there are exceptions but these aren't important at this point). So with every cell containing a back-up copy of DNA, how can cancer take root?

During every hour of your life, millions of your cells die. Don't worry, this is a perfectly natural process. For example, the cells that line the gut are continually shed due to the harsh environment of the digestive system. Fortunately, these cells are replaced at exactly the same rate that they die resulting in no net change in cell number. We need to keep turning over cells because they wear out or become damaged. We are continuously exposed to damaging agents such as chemicals and solar radiation that bombard our cells and damage our DNA. When this happens the cell attempts to repair the damage. Each cell has an army of proteins that are experts at recognizing damaged DNA, cut out the broken pieces and stitch in a new piece of DNA, much like repairing potholes in a highway. But these repair crews are not perfect. Sometimes they make mistakes. Sometimes they fall asleep on the job and fail to notice the damage.

To replace dead cells, other cells must reproduce themselves. To do this they have to be triggered by appropriate signals. They then undergo a series of events in which they increase in size, copy their DNA content, sort the newly duplicated chromosomes

into opposite ends of the cell and then divide from one big cell into two smaller cells. At each step supervisor proteins check that each process has been properly executed. If it has, the cell is allowed to go to the next step. These supervisors look out for bits of DNA that result from unrepaired damage or errors introduced during the photocopying of the DNA during the replication process. If they detect a problem they pull the plug and shut down the cell. If the damage is irreparable, the cell quietly commits suicide. This happens all the time. Since we are made up billions of cells, we can afford to lose a slew of imperfect examples. If we let one of these through the replication process, however, we generate mutant cells. Such mutants don't know they are defective and if they did, they wouldn't know which of the two copies of the affected DNA was correct and which was incorrect. For this reason, there are many checks and balances required for a cell to successfully divide into two.

Over the past twenty years, our understanding of the changes that occur during development of cancer has been vastly improved. We know that it takes several (five or six) independent events or mutations. That's why the chance of developing the disease increases with age. It takes time for such events to accumulate. There is also a continual process of selection and evolution. Most mutations have no relevance to cancer. They are either silent or they actually lead to cell death. But some mutations confer a slight advantage to a cell compared to its surrounding cells. It may divide a little faster. It may process fuel more efficiently. It may be deaf to certain signals that shut cells down. It may think its getting a "let's multiply" signal when there is none. It may have a defective DNA repair component. The possibilities are numerous but if there is a competitive advantage, children of such cells will start to overgrow the normal cells.

At this stage there is nothing to see. Since many of our tissues are constantly renewing themselves a microscopic overgrowth is undetectable. However, as the number of mutant cells increases, other pressures come to bear. The immune system may notice something odd and start killing the cells. The nascent cancer may be eliminated. However, some of the cells (maybe just one) may have developed a new mutation that allows it to slip past the immune police. It then steadily and slowly repopulates and replaces the killed cells. Now all of these cells are invisible to the immune system. There may now be more than a million mutant cells - still hardly visible to the eye. Like any cells, the new tumour cells need food and oxygen to grow. After a certain size, these become limiting because the distance between the cells in the middle of pinhead sized tumour becomes too great for efficient transport of nutrients. Cells begin to starve to death and the growth becomes self-limiting. If it grows beyond a certain diameter the cells at the core die. Unfortunately, additional mutations often occur which trick blood vessels into thinking the tiny tumour is perfectly normal. The blood vessels become attracted to the growth because the tumour cells start making molecules that the blood vessel cells find irresistible. This process mimics a natural process that has to occur as a foetus grows. The blood vessels are subverted into supporting cells that have no intention of repaying their kindness. This process of attracting new blood vessels is called angiogenesis and, in a clever manipulation, offers a promising Achilles heel for new anti-cancer agents (see part 2).

The tumour is now growing at an increasing rate. It's engineered its own plumbing and waste-disposal system, it isn't hampered by the normal chores of providing services to its host body - its become a free-riding, tax-dodging, small-time thief. But cancer cells aren't malicious. They aren't out to kill their host. They are entirely ignorant of the havoc they wreak. As their growth rate increases, so does the frequency of error accumulation in the DNA. The tumour is no longer a clump of identical cells. Each is slightly different, housing a variety of mutations. At this stage in its development the cancer may be quite easily cured. This is because it is localized. It's trapped within the part of the body in which its ancestors were born. But the cancer soon learns to make protein wire cutters that chew through the fences holding it in place. When this happens, the cells of the cancer can move into the blood system. The result is akin to giving 50 people TTC tickets but forgetting to tell them where to get off. The mutant cells disperse all over the body. Most that do this die because they run out of energy or fail to find safe housing. But some lodge in new areas and settle down. Some begin to grow. Once a cancer spreads from its original home the treatment options become limited. This spreading process is called metastasis.

How does cancer kill people? Rarely does the initial cancer threaten life. Exceptions are when the cancer is growing close to a particularly important functional centre such as a part of the brain that controls breathing or block blood flow to a critical organ. Usually, cancer kills by slowly overwhelming the body, by interfering with normal functions, by slowly choking off the bodies supplies. Left to their own devices, cancers may kill within months or may take years. Rarely, a cancer may spontaneously regress and disappear. We have three main weapons against cancer with new tricks coming along. The big three are surgery, radiotherapy and chemotherapy. The first two options are only effective if the cancer has not spread since no surgeon can scan the entire body for microscopic escapees. Over the past thirty years, each of these tools has been steadily improved. Surgery is commonly far less radical, that is, less tissue is removed. Lumpectomies have largely replaced mastectomies, for example, in treatment of breast cancer. Such advances have been made possible by combining two or three modes of treatment. Lumpectomies are usually accompanied by radiotherapy and sometimes with chemotherapy as well (depending on the information determined by the pathologist). Radiotherapy has become more accurate. Using complex instruments and imaging technologies, precise targeting of the tumour can be accomplished reducing the dose of radiation needed. Radiation kills cells by causing irreparable DNA damage. Therefore it can also contribute to cancer and can also cause scarring and burns which is why using as little as possible is important. We have a plethora of chemotherapy drugs most of which are now used in complex combinations that have been determined to maximize effectiveness. Most of these drugs also kill tumour cells by damaging DNA. Moreover, these chemotherapy agents don't specifically target cancer cells, they target any rapidly dividing cell. That's why many chemotherapeutic drugs have lousy side effects. They can also kill the cells that line the gut, hair follicles and bone marrow cells resulting in intestinal problems, alopecia (hair-loss) and anaemia.

If we have all of these tools, why do people still die of cancer? Often the treatments are successful and the tumour seemingly disappears. But then, 1, 3, 6 or more years later, it may reappear and sometimes may be more aggressive and resistant to drugs that were effective the first time. Although relapse, as cancer re-occurrence is called, is poorly understood, it is due to failure to kill every single cancer cell at the first presentation. Some cancer researchers think that most tumours undergo a degree of metastasis that is undetectable. The dormant, mutant cells bide their time until some unknown trigger reawakens them. Since they've survived the original treatment, perhaps they've accrued mutations that protect them from chemotherapy drugs. It is also important to remember that we are surrounded by cancer survivors. The disease can be beaten but we need to improve the odds. Cancer is a terrible disease but progress is being made. The sneaky target is forever moving, changing and hiding but around the

world research is tackling every element of cancer. Indeed, we hear about promising breakthroughs almost every day. In the next article I will describe the research process, who does it, how they are regulated and why today's wonder drug is often tomorrow's disappointment.

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