The Basic Science of Colon Cancer

The Cell

I have always believed that to understand what really happens to the body when it is stricken with disease you have to have some basic understanding of biology as well as human anatomy and physiology. Unfortunately, discussing such subjects can be rather dry and complicated. During such discussions my patients often echo my wife, who is fond of saying, "Just tell me the time, not how to build a clock." Even as I considered writing the *Cancer Answers* series, I was still struggling to find useful metaphors and imagery to assist my patients and possible readers in grasping the biologic principles that are critical to understanding how cancers begin and grow. Divine providence seemed to intervene when my then 7-year-old son, Daniel, asked if I would speak to his second-grade class. He explained that the class was completing a study unit entitled "Jobs," and parents were encouraged to visit the class and talk about their work. After a pregnant pause, I told him I was delighted to speak, but I was not quite sure whether talking about cancer was appropriate for 7 year olds. Daniel assuaged my concerns by relating that other parents who were physicians had already presented. One child's mother explained how she kept sick people asleep while they had surgery, and another child's father talked about how he helped people to breathe better. The gauntlet was thrown: if an anesthesiologist and a pulmonologist could do it, then so could a medical oncologist. I contacted Daniel's teacher and arranged my visit. The day approached, and I was beginning to panic that there was just no way to explain cancer to 7-year-old children. To have any hope of understanding cancer and its treatment, you have to understand that animals are made from cells, that cells can transform

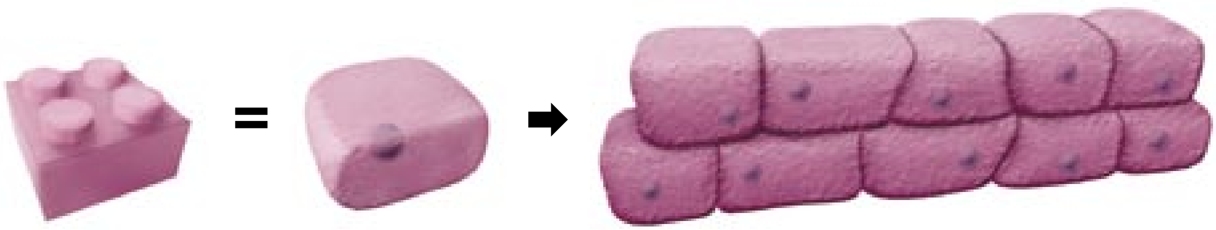

Figure 1-1 The Lego—the Perfect Metaphor for the Cell

and grow out of control, and that medicines are available that can kill these transformed, bad-behaving cells without harming the good cells that keep us alive. Unfortunately, these kids were in second grade and did not even know what a cell was.

I went to Daniel's bedroom to confess my dilemma. Daniel was on the floor with his Legos splayed about him. When I saw the hundreds of Legos in every color, shape, and size joined in various ways to create cars, houses, and planes, I had an epiphany. The Lego was the perfect metaphor for a cell (Figure 1-1).

In Legoland, the Lego is the basic building block. Hundreds of different types of Legos when appropriately combined can create an infinite variety of structures. You can take Legos of just one variety and stack them side by side and up and down to create a wall. Add two windows and a door, and create the completed front wall of a house. After a child builds three sidewalls and secures them with a floor and a roof, the house takes on a recognizable appearance. Eureka, my problem was solved (Figure 1-2).

I explained to Daniel that while the Lego is the basic building block of Legoland, the cell is the basic building block of organic life (living creatures). The cell is called the origin of life because animals grow from a single cell made by the joining of sperm and egg. One cell gives rise to the billions of cells that make the complete animal. Like Legos, the billions of cells are not identical in appearance but rather fall into a few hundred different types: hair cells, skin cells, blood cells, etc. (Figure 1-3).

Figure 1-2: Assorted Legos

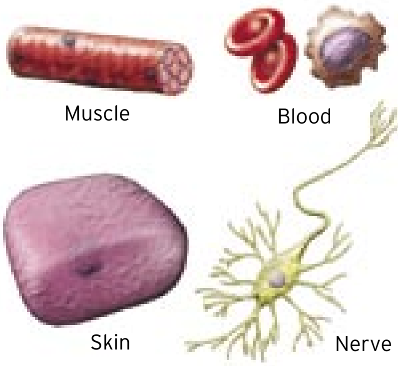

Figure 1-3: Assorted Cells

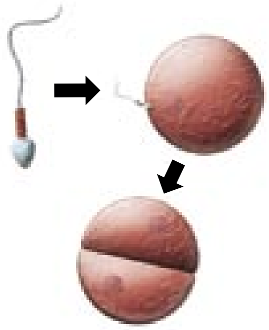

Figure 1-4:
The Origin of Life

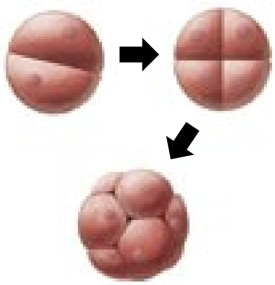

Figure 1-5:
Cellular Division

The formation of the human body, like any mammal's body, begins with the meeting of a sperm and an egg. The sperm fertilizes the egg, which creates the first cell, the beginning of a human body (Figure 1-4). This cell then divides to make two cells. Two cells divide to make four, and then those cells continue to divide until there is a cluster of cells (Figure 1-5). Initially, all of the cells in the cluster are identical. Next these identical cells begin a process in which they become the more than 200 different types of cells that make the human body complete. This process is called DIFFERENTIATION; the cells differentiate or become different types. This early developing human is called an EMBRYO.

The process of differentiation in the developing embryo begins with these clustered cells organizing into three layers: an outer layer called ECTODERM, an inner layer called ENDODERM, and a middle layer called MESODERM. These three layers of cells are in turn encased in a layer of cells that will give rise to the placenta. The outer of these three layers, ectoderm, differentiates into skin and nerve cells. The middle layer, mesoderm, differentiates into blood, muscle, and bone cells. The inner layer, endoderm, differentiates into the cells that comprise all of the body's organs (Figure 1-6).

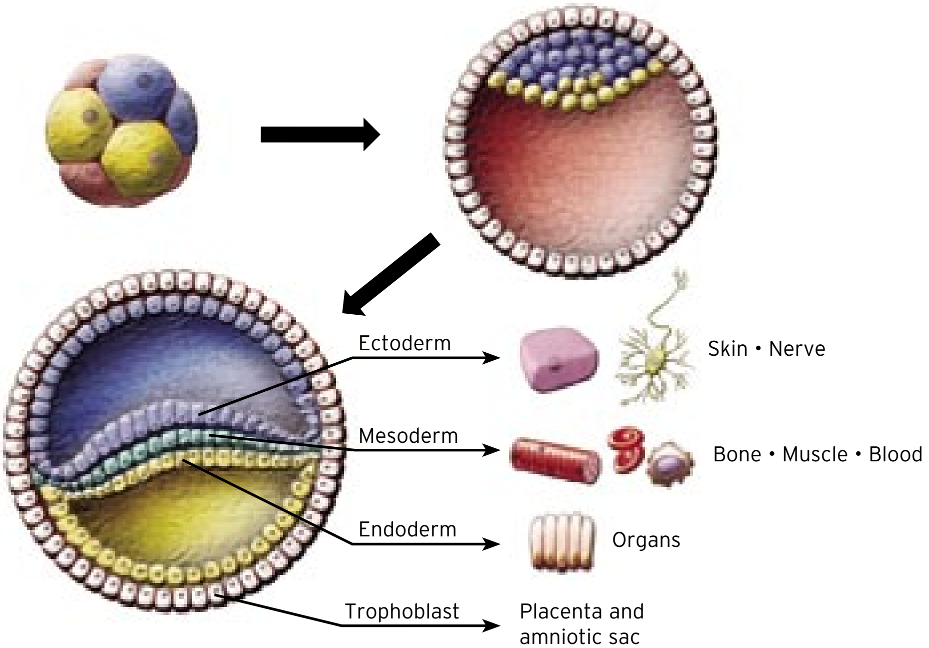

Figure 1-6: Cellular Differentiation

Imagine Legoland being alive. In the beginning, there was one small, rectangular, white Lego. Then there were a bunch of small, rectangular, white Legos; then white Legos morphed into three groups—white, red, and blue rectangles.

Primitively speaking, all of your body's organ cells begin with the endoderm layer: they have a common origin and are structurally similar. This is a very important point, as we will later see. As these primitive cells further differentiate and mature, their structure and function assume that of adult cells. Mature cells progress from individual cells to sheets of cells. The sheets of cells then organize to form TISSUES. Different types of tissues combine to form organs. Finally, the organs are arranged within a musculoskeletal framework supported by a circulatory and nervous system.

Returning to our Legoland metaphor, the white, blue, and red Legos have now morphed into hundreds of different types. There are billions of each type, trillions of Legos in all. Some Legos have been assembled into a wall (like sheets of cells forming tissues). Doors and windows have been added to the wall to make the front of a house (like an organ), and roofs, floors, walls, and more have been organized to make a complete house (like a complete human being).

Daniel was an attentive and courteous listener as I expounded gleefully, progressing from Legos and cells to cancer and treatment. When I finished my diatribe, gratified to have found the long-sought metaphor, I asked Daniel what he thought. He said that he liked the Lego part but that I definitely needed to bring some kind of neat machine, like the breathing thing with the balls that go up and down that the lung doctor demonstrated. Also, I needed to bring a give-away such as gloves or masks or maybe pencils with my name on it. I left Daniel's room defeated, feeling small and humbled. I went to my office with hopes of finding something appropriate to give 15 second graders, mired in thought of what kind of cancer machine I could demonstrate.

The Colon: Normal Structure And Function

Doris and Sam were among the first patients to see my Legos demonstration, and it was a success. Not only did they not think I was crazy, but it helped them to understand cells. The next step was to explain why humans have colons and what kinds of cells comprise them.

Unlike the Legos that I have been using for illustration, cells not only have structure, they also have function and are alive. To stay alive, cells must eat and breathe; blood provides the oxygen and nourishment. The body, like the cells that comprise it, also needs to eat and breathe. The food that's ingested for nourishment has to be broken down or DIGESTED into essential nutrients (fats, carbohydrates, and proteins) so they can be absorbed into the blood and transported to the cells in need. The organ system that facilitates the digestion and absorption of nutrients is referred to as the GASTROINTESTINAL SYSTEM or GI TRACT (Figure 1-7).

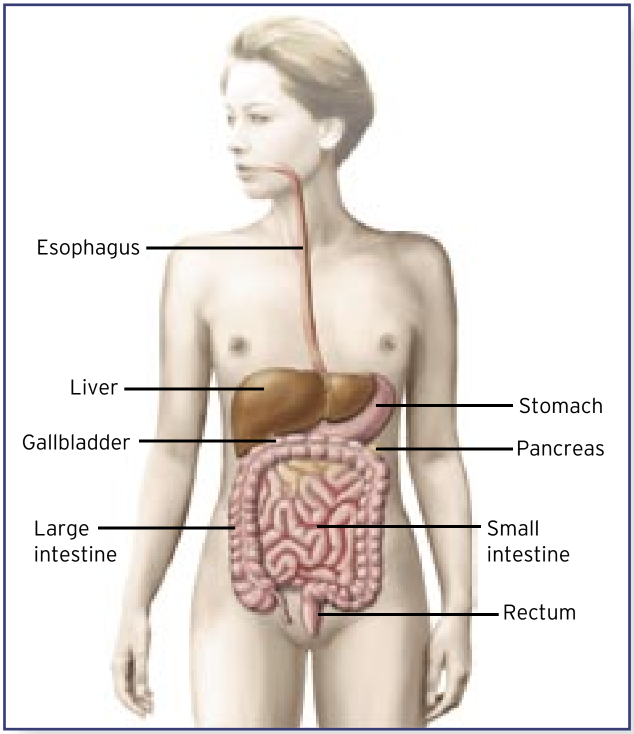

Figure 1-7: Gastrointestinal System

The colon and rectum are key components of the GI tract (with the small INTESTINES they comprise the colloquially referred to BOWEL that gives rise to BOWEL MOVEMENTS). The basic biology and function of the colon and rectum may be better understood if we understand what happens to the food we eat as it passes through the digestive organs. The food entering the mouth is met with saliva, a mildly acidic liquid that also contains chemicals called DIGESTIVE ENZYMES. The saliva production was triggered in the brain by the thought, sight, and smell of food. The digestive enzymes and acid in the saliva, in conjunction with chewing, begin the digestive process. When chewed food is swallowed it is transported to the STOMACH through the muscular tube called the ESOPHAGUS. The muscular component is present throughout the organs of the GI tract as the nutrient-rich food and later nutrient-poor waste is propelled forward by a sequential squeezing motion, a process called PERISTALSIS (imagine a mouse traveling through a snake). Once in the stomach, the minimally digested food is exposed to a harsh environment with greater acidity and more digestive enzymes. The food will reside for a time in this acidic and enzyme-rich milieu to continue the process of decomposition. The food is prevented from re-entering the esophagus by a muscular valve called the ESOPHAGEAL SPHINCTER, and it is held in the stomach by another muscular valve called the PYLORIC SPHINCTER, which controls its exit.

Immediately upon exiting the stomach, the partially digested food enters the SMALL INTESTINE. In the first of three portions of the small intestine, the nutrient-enzyme-acid mix is augmented by more digestive enzymes from the PANCREAS as well as BILE from the LIVER. The bile is stored in the GALLBLADDER, unless gallbladder disease, usually stones, has previously necessitated surgical removal. In the presence of the many enzymes, bile, and denaturing acid, the nutrient-rich slurry is reduced to its most basic components of proteins, carbohydrates, and fats. In the 30 or so feet of intestine (divided into three anatomically distinct sections: DUODENUM, JEJUNUM, and ILEUM) the body uses MUCOSA (specialized cells lining the inside surface) to ABSORB or take in the nutrients from the digested food. The loops and loops of small intestine end in the lower right quadrant of the abdomen where the small intestine or UPPER GI TRACT transitions into the COLON, also referred to as the LOWER GI TRACT, LARGE BOWEL, and LARGE INTESTINE. Two distinct anatomic structures, the APPENDIX and the CECUM, identify this transition region at the end of the ileum and the start of the colon. The nutrient-rich food consumed hours ago has now traversed the esophagus, stomach, and 30 feet of small intestine. During this journey, food was depleted of nutrients leaving only water and waste, like indigestible plant fiber, to be propelled through the colon via peristalsis.

Similar to the small intestine, the colon is divided into sections or segments.There are five segments in all. The first segment, or ASCENDING COLON, acquired its name because when one is standing, the material within it, waste and water, is propelled up or ascends from the lower right to the upper right abdominal quadrant. To use the correct anatomical-speak, the ascending colon transports waste and water from the ileum to the TRANSVERSE COLON, the second portion of the colon. The transition from ascending to transverse colon is marked by a 90-degree turn just below the liver, an anatomic refer-

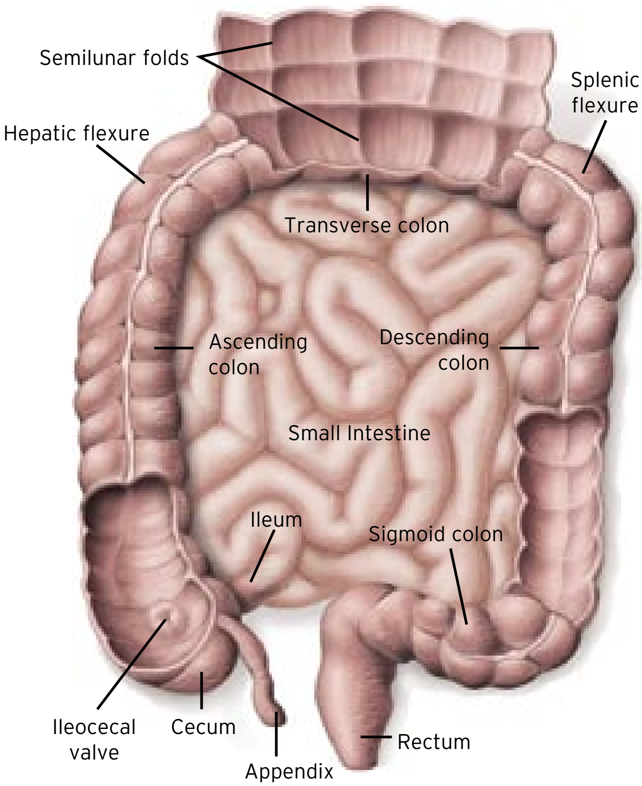

Figure 1-8: The Colon and Rectum

ence point referred to as the HEPATIC FLEXURE. The transverse segment of the colon crosses the upper abdomen from right to left. In the upper left abdominal quadrant, the colon once again takes a 90-degree turn anatomically referred to as the SPLENIC FLEXURE, which marks the next transition. The colon then descends (if one is standing) in a straight line toward the left hip; hence this third portion of the colon is called the DESCENDING COLON. The end of the descending colon, just above the left hip, is the fourth transition point. Here the colon leaves the abdominal cavity and enters the PELVIC CAVITY, taking on an s-shape to curve around other anatomic structures (like the bladder). The name of this s-shaped segment comes from the Greek letter, sigma, and is thus called the SIGMOID COLON (Figure 1-8).

Throughout this journey, which follows the periphery of the abdominal cavity, the specialized mucosal cells lining the interior of the colon have been busy removing the one critical nutrient not claimed by the small intestine, water. By the time the digested food reaches the cecum, all of the nutrients have been resorbed, leaving only waste and water. After the entire colon has been traversed and the water reclaimed, all that remains is waste. As the sigmoid colon enters the PELVIS, it transitions once again, this time into the RECTUM, a reservoir for waste. Another muscular valve or sphincter permits voluntary evacuation of waste from the rectal vault, a process technically referred to as DEFECATION. This valve is called the ANAL SPHINCTER. An intact anal sphincter permits voluntary defecation referred to as BOWEL CONTINENCE, but if the sphincter is damaged then waste leaks uncontrollably, referred to as BOWEL or FECAL INCONTINENCE. The anal sphincter is the anatomic landmark for the final transition connecting the rectum to the outside, through an orifice or opening called the ANUS.

At this point in my presentation, I could tell Doris and Sam were perplexed by my insistence that we take this virtual tour of the GI tract. I explained that to understand the location of the cancer, its cause, the therapy needed for cure, and possible side effects of treatment, it was necessary to understand the anatomy. They refocused as I posed a question. "When you look at yourself in the mirror you might distinguish your chest from your abdomen but can you distinguish your abdomen from your pelvis?" I offered, "You might get a bit of help figuring out where your pelvis is positioned by sitting down: The part of the body that you saw in the mirror when you were standing but is now obstructed from view by your legs is your pelvis." The PELVIC or PERINEAL CAVITY is anatomically distinct from the ABDOMINAL or PERITONEAL CAVITY. The abdominal cavity contains most of the colon, all the small intestines, and the other organs of digestion as well as the liver, spleen, and kidneys. The pelvic cavity is a basin or bowl-shaped cavity created by your hipbones and lower backbone that forms the end of your body's trunk. The organs encased and protected by this bony cavity include the rectum, the bladder, the male prostate, and the female uterus, ovaries, and fallopian tubes. The skin surface between the thighs, where the rectum via the anus, the bladder via the urethra, and the genitals communicate with the outside is referred to as the PERINEUM.

Having reviewed the entire gastrointestinal tract from appetite to anus and learning the differences between the abdomen and pelvis Doris and Sam were ready to understand the relationships of the colon and rectum to the rest of the three-dimensional abdomino-pelvic anatomy. To understand these relationships, visualization techniques will help but, first we need some directional keys. Doctors realized early on that since the body is three dimensional, describing up or down can get confusing, i.e., when standing, up might be toward the head and down might be toward the toe, but when lying down, up may be toward the belly button and down may be toward the buttocks. Rather than up/down or front/back, the anatomy teachers came up with a more accurate map key for the body. Toward the head is referred to as CEPHALAD. Toward the feet is referred to as CAUDAD. Toward the front of the body (belly button, chin) is ANTERIOR while toward the back (spine, buttocks) is POSTERIOR. When we describe something located toward the midline we refer to it as MEDIAL, and that which is located away from the midline is referred to as LATERAL. Finally we need a way to explain positions relative to a point of anatomic interest. Regarding a segment of colon, the end that is closer to the small intestine is PROXIMAL, whereas the end that is closer to the anus is DISTAL; e.g., the rectum is distal to the sigmoid colon but proximal to the anus (Figure 1-9).

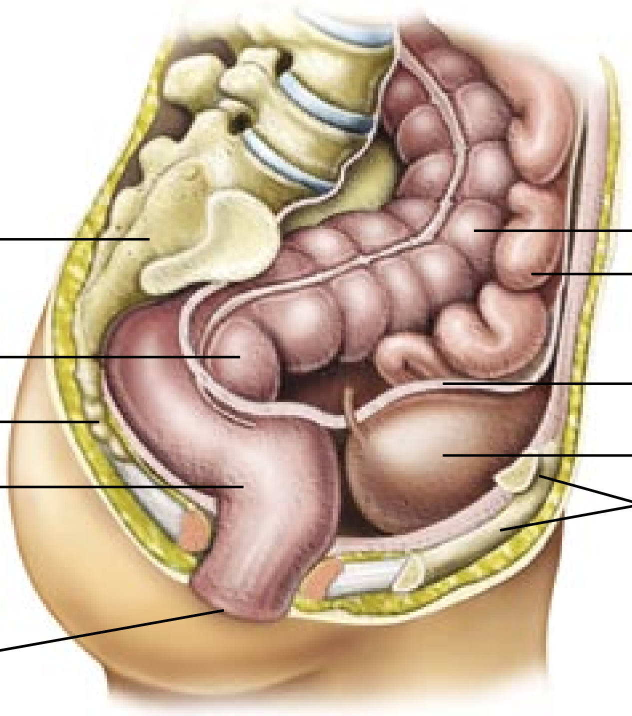

Figure 1-9: Abdominal and Pelvic Cavities

Our next task is to try to visualize the abdomen from top to bottom or cephalad to caudad. You might think of the colon as a 6-foot length of garden hose lying under the skin and muscle of your belly or, in correct anatomic speak, the anterior abdominal wall. It's positioned in a horseshoe shaped arch with the points down or caudad. The horseshoe outlines the periphery of the abdomen with the right arm of the horseshoe (ascending colon) beginning just above the right hip bone, the arch of the horseshoe (transverse colon) following along the diaphragm and the left arm of the horseshoe (descending colon) parallel to the right ending at the left hip bone. Lying within the borders created by the horseshoe is a layer of connective tissue like the webbed pocket of a baseball glove, called the MESENTERY (Figure 1-10).

Let's now try to image the abdomen front to back, or in correct anatomic speak, anterior to posterior. The colon and intestines sit against the anterior abdominal wall in the anterior abdominal compartment. Behind or posterior to the colon and intestines lie the kidneys and ureters. Posterior to the kidneys lay the major blood vessels of the trunk, the main artery AORTA and the main vein VENA CAVA. The posterior wall of the abdomen is defined by the backbone and supporting muscles.

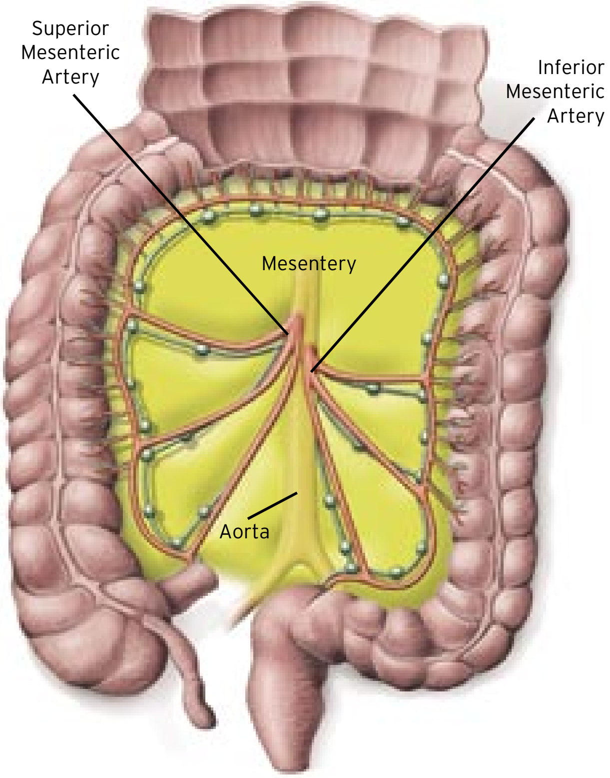

Figure 1-10: Colon and Rectum with Mesentery and Circulation

The sigmoid colon arises from the left end of the horseshoe coursing both caudad, toward the crotch (not an accepted anatomic term), as well as posterior, toward the backbone, as it leaves the abdomen and enters the pelvis. The rectum resides strictly within the pelvis. This completes our lesson in gross anatomy. It's gross not because it's icky but because we're referring to the anatomy as it looks to the unaided eye before it's dissected and placed under a microscope (just like your paycheck is gross before it's dissected with taxes and deductions).

With the images of the gross anatomy of the gastrointestinal tract now etched in your memory we are ready to look beneath the surface at the structures not visible to the naked eye. We begin our discussion of microscopic anatomy by visualizing the tissues that comprise the colon and rectum.

All of our organs have specialized cells that perform the unique functions that define them. There are specialized cells in the breast that make milk, there are specialized cells in the pancreas that produce insulin and digestive enzymes, and there are specialized cells in the intestines that permit the absorption of nutrients. These specialized cells comprise the GLANDULAR TISSUE of the organ and require a host of other supporting tissues necessary for their function. The specialized cells of the colon permit its unique operation to reclaim water.

Under low-power magnification, the microscope reveals the colon not to be a simple 5- to 6-foot garden-hose-like tube but rather a complex multilayered cylindrical structure. Three main layers are apparent, the outer protective membrane or SEROSA, the more substantial muscular layer or MUSCULARIS that facilitates peristalsis, and the innermost layer or MUCOSA, which is comprised

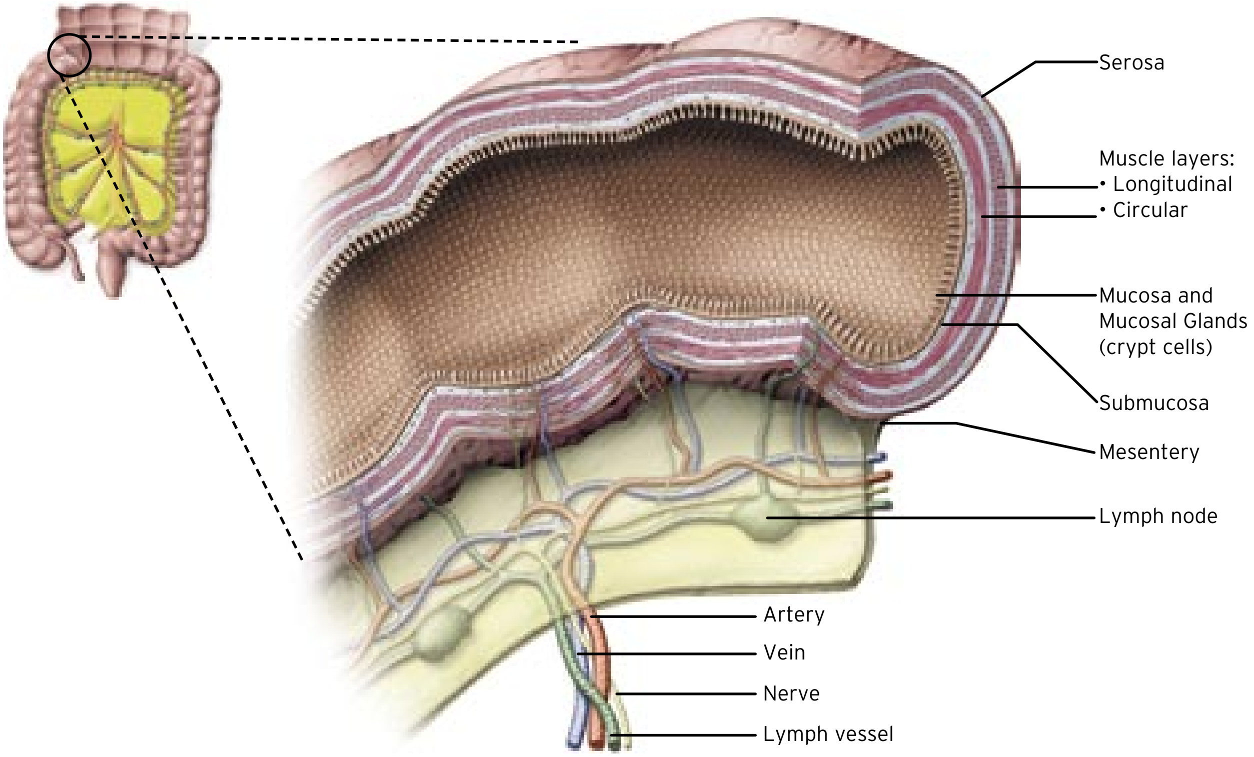

Figure 1-11: Low Power Magnification of the Colon

of the specialized glandular tissue that facilitates the absorption of water. The muscle layer creates an appearance of centipede-like segmentation called HAUSTRA, visible both on the outside and inside of the colon, but the colon remains hollow throughout (Figure 1-11).

The diseases referred to as colon cancer develop in the mucosal layer of the colon. Both men and women have colons and are equally exposed to the agents that promote colonic mucosal cell transformation to cancer. Before we can begin to understand how and why the mucosal cells transform we need to delve a bit deeper into the microscopic anatomy of the colon. We must visualize the cellular layers that permit the colon its unique function of water reclamation.

The mucosal lining appears smooth to the unaided eye but under the microscope we see that the mucosa is more like a brush with tightly packed, short bristles. The spaces or valleys between the bristles of the brush are called CRYPTS where the water reclamation work occurs. The waste and water are propelled by peristalsis across the top of the bristles of the brush allowing the water to collect in the crypts where it can be absorbed by the CRYPT CELLS. Below the layer of crypt cells lie the small blood vessels into which the absorbed water is transferred.

Doris and Sam were patient listeners as I conducted this lesson in anatomy with my words and pencil drawings. They were ready for the next lesson when I would explain how these normal colon crypt cells are transformed into cancer.

Carcinogenesis

Throughout your lifetime cells are continuously injured and repaired. Bruises, scrapes, cuts, burns, infections, chapped lips, and tongues burned by pizza cheese and hot coffee are a sample of the myriad of everyday cellular injuries that you experience. Your body has the remarkable ability to repair this cellular damage and does so in a constant, ongoing process. Some cellular damage is below the surface, caused by the tobacco smoke that we inhale, the chemicals in the food that we eat, the radiation from the sun, and the internal (natural), physical, chemical, and hormonal stresses that are part and parcel of being alive. Sometimes, if the injuries are chronic or recurrent, or if there is a genetic predisposing defect, the body is unable to repair the cellular injury. The body's failure or inability to repair cellular injury can lead to cancer. The process by which the failed repair of cellular injury leads to cancer is called CARCINOGENESIS.

In the beginning of this chapter, I mentioned that all of the body's specialized organ tissue has a common origin in the cells of the endoderm of the developing embryo. As these primitive cells mature, they retain certain common features, giving organ tissue a similar appearance under the microscope. The microscopic appearance is often referred to as GLANDULAR, which means something different than what you might think. To a PATHOLOGIST, glandular tissue refers to a group of cells that are organized so that they can either take in nutrients (absorb) or release chemicals needed to maintain normal body function (secrete). The cell type common to these glandular tissues is called an EPITHELIAL CELL. The epithelial cells are flat where they connect the organs to the outside, such as at the mouth and anus; are cube-shaped in the organs that are secretory, such as the breast, prostate, and pancreas; and are an elongated cube or column shaped in the organs that absorb nutrients, such as the colon

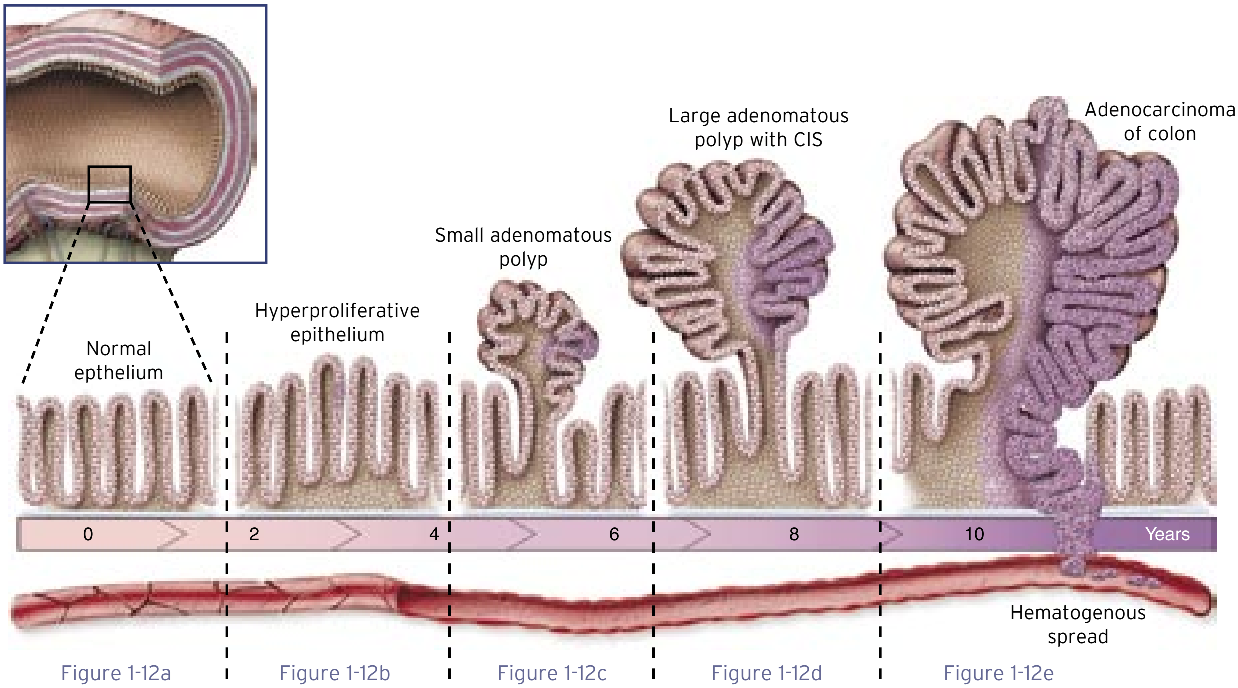

Figure 1-12a–e: High Power Magnification of Colonic Mucosa with Time Sequence of Carcinogenesis

and small intestine. When flat epithelial cells transform into cancer, they are called SQUAMOUS CELL CARCINOMA. When cuboidal or columnar epithelial cells transform into cancer, they are called ADENOCARCINOMA.

The glandular tissue of the colon is comprised of the colonic mucosa and its crypt cells (Figure 1-12a). Researchers have begun to unravel the mystery of the genetic, molecular, and cellular changes that lead to the carcinogenesis of colonic mucosal tissue. As I explain later in Chapter 1, these injuries are not superficial and are not on the surface of the cell. Rather, these changes occur deep within the guts of the cell, in its nucleus and its DNA, changing the cell's appearance, behavior, and very essence. They can turn a cell from a well-behaved and orderly Dr. Jekyll into Mr. Hyde, wreaking havoc and chaos. The process of transformation from Jekyll to Hyde is predictable, often slow, but relentless.

The transformation of colonic mucosal cells into cancer, is referred to as ADENOCARCINOMA OF THE COLON. The process begins with the physical and chemical stress on the mucosal cells, as they function continuously to reclaim water from the food we ingest. These chemical stresses may come from CARCINOGENS in the food we eat, from the bile acids that assist in the digestion of food, and/or from the bacteria that live within us. These stresses lead to irritation and then injury of the mucosal cells. If the body is unable to repair the injured cells, new cells are added to the injured ones, resulting in an overgrowth of mucosal cells, which is called HYPERPROLIFERATIVE (Figure 1-12b).

As the mucosal cells continue to overgrow, they become unstable, altering their appearance and behavior. The cells become larger and less uniform, their growth pattern less organized. Continued stress, cellular injury, and repair process mistakes result in what are called MUTATIONS (physical changes in cellular DNA described in more detail later in this chapter), which lead to the creation of more aggressive cells. These more aggressive cells may so overgrow that they create a mound. The mound may be flat or it may be mushroom-like. The cellular mound, called a POLYP, may become large enough that it can be felt on examination (if in the rectum), interfere with passing feces, bleed, or be visualized through an endoscope. At this point, pathologists call the overgrowth ADENOMATOUS (Figure 1-12c). Additional mutations may result in these adenomatous polyps developing CIS (CARCINOMA IN-SITU) the earliest form of cancer (Figure 1-12d).

Unfortunately, patients do not always experience or observe changes in their stool caliber or color, observe blood in the stool, develop symptomatic anemia from bleeding, or undergo routine screening exams (discussed in detail in Chapter 2). If CIS remains undetected, the next cellular event that can occur is an even more aggressive change. These unstable, mutated mucosal crypt cells that have met the first criterion of cancer by their pattern of overgrowth no longer respect the boundary of the mucosal layer. They invade or infiltrate through the mucosa (visualize a tree root growing through the street or sidewalk). This INFILTRATING tumor, or INVASIVE colonic adenocarcinoma, is the most advanced form of cancer within the colon and or rectum (Figure 1-12e).

The more I explained to Doris and Sam, the more questions they had. Doris was confused: She didn't smoke, she ate a well-balanced diet and she exercised everyday. Sam chimed in, "She eats like a bird, how could she have developed a cancer in her rectum?" I advised a deep breath and patience because I was just about to explain how normal, everyday stress could cause cellular injury and initiate the cascade of events that result in cancer. In order to understand the how and why of carcinogenesis, one needs to understand the inner workings of a cell—its GENETIC CODE.

Genetics

All human cells have a similar design: an outer membrane covering a gelatinous liquid cytoplasm within which is a central core structure, the nucleus. The image is that of a Tootsie Roll Pop where the wrapper is the cell membrane, the lollypop candy is the cytoplasm, and the Tootsie Roll is the nucleus (Figure 1-13). Within the nucleus resides the blueprint or operating code of not only the cell but also of the entire organism.

Figure 1-13: The Cell as a Tootsie Pop

Like computer software written in special binary code, the operating code of living organisms is written in a special language called DNA, which is actually a chemical code comprised of four characters called NUCLEOSIDE BASES. DNA is a unique code language that, once translated, instructs the cell to build PROTEINS. Proteins are the cell's machines that bring food into the cell, remove waste from the cell, repair the cell after injury, prepare the cell for growth and division, etc.

Like many other types of machines that we are more familiar with, proteins may have many different functions but are all structurally related. Automobiles, tractors, speedboats, and helicopters are very different forms of transportation but are all propelled by an internal combustion engine. Refrigerators, blenders, washers, and coffee grinders are very different appliances, but they are all powered by an electric motor. Computers, cell phones, digital cameras, and CD players perform different functions, but they are all controlled by a microprocessor chip. Like each of these examples of inorganic machines, proteins are the workhorses of organic machines and the cells that comprise them. The blueprint for each protein is encrypted in the DNA code.

By definition, a code must be broken or translated for the encrypted message to be understood. The DNA message for protein building requires not only translation, but it must also get transported from the nucleus to the cytoplasm where the proteins are manufactured. The translation and subsequent transport of the encrypted DNA message is facilitated by another nucleoside base language called RNA. The DNA message is translated to RNA, which leaves the nucleus and travels to the cytoplasm where it docks with a structure called a RIBOSOME, the protein-manufacturing factory.

The chemical building blocks of proteins are called AMINO ACIDS. The amino acids are chemically linked one to another according to the instructions of the DNA message. Let me try to summarize in a single statement: *Amino acids in the cytoplasm are assembled into proteins by the ribosome under the direction of an RNA message, which is the translation of a DNA code sequence from within the nucleus* (Figure 1-14).

A complete DNA sequence that encodes a protein is called a GENE. Genes are clustered into long strands of DNA called CHROMOSOMES, which are made even longer because these genes are also separated from one another by non-message base sequences. There are 46 chromosomes in a normal human cell, 23 contributed by the father via the sperm and 23 contributed by the mother via the egg. The chromosomes are arranged in 23 pairs. Scientists now believe that there are between 20,000 and 40,000 genes necessary for human life, making it likely that there are approximately 1,000 to 2,000 genes per chromosome pair.

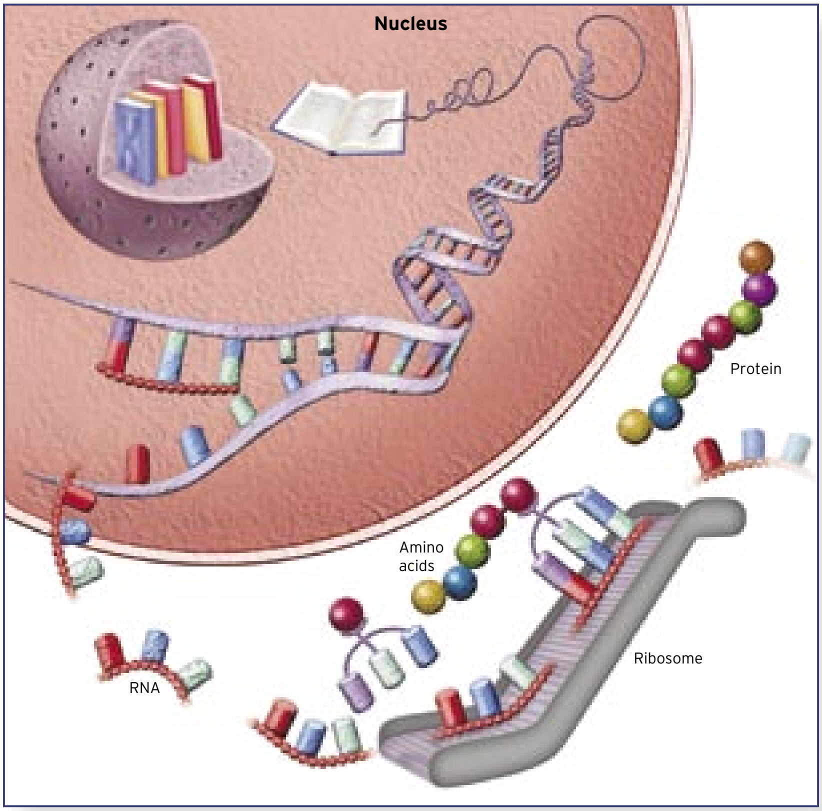

Figure 1-14: The Biochemical Basis of Life: DNA-RNA-Protein. Amino acids in the cytoplasm are assembled into proteins by the ribosome under the direction of an RNA message, which is the translation of a DNA code sequence from within the nucleus. Every cell in the body has the complete manual of information (genome) stored in its library (nucleus).

Think of this genetic operating system or GENOME as the body's complete information encyclopedia or better still, the body's owner's manual. Everything needed to build, operate, and repair the body is written in the manual, a copy residing in each cell. The encyclopedic size owner's manual is comprised of 23 volumes (chromosome pairs), each 1,000–2,000 chapters long (genes) composed in a four-character code language (DNA) requiring billions of characters (nucleoside bases) in all. *Every cell in the body has the complete manual of information (genome) stored in its library (nucleus)*, but only certain volumes are off the shelf at any one time, opened to specific chapters as the genetic needs dictate. Genes for hair color would not be turned on in blood cells, and genes to produce HEMOGLOBIN would not be turned on in hair cells. Beginning in the embryo and throughout cellular differentiation, fetal maturation, growth, and development, messages are turned on and off in a complex system of signals and responses. For the messages and signaling to work properly, every cell needs to have its billions of characters (nucleoside bases) in the correct sequence, ready for the moment when one of the volumes is taken off the shelf and opened to a chapter to be translated. A mistake in a base sequence is called a MUTATION.

Mutations can occur in a variety of ways. Let's use that encyclopedic owner's manual metaphor to illustrate the point. Sometimes information passed on from a parent is incorrect, causing some of the chapters to have wrong information. Such genetic mutations are called HEREDITARY MUTATIONS. Sometimes there is a misprint at the factory (embryo or fetus), leading to incorrect information in some of the chapters. Such genetic mutations are called CONGENITAL MUTATIONS. Most commonly, the original information and printing are correct, but from years of use and handling, print becomes smudged, paper stained, or pages torn, leading to incorrect messages. Such genetic mutations are called ACQUIRED MUTATIONS.

Genetic defects or mutations that cause a cell to reproduce uncontrollably and invade surrounding structures are what cause cancer. Many forms of cellular injury like those caused by chemicals and radiation lead to the types of mutations that cause carcinogenesis. Acquired mutations rarely occur from a single insult but rather from repeated insult and injury like years of tobacco use, chronic irritation from fecal waste, decades of cyclic hormonal stress, or just living. Thus, all cancers are consequences of genetic mutations, but few, approximately 10%, are hereditary. Most cancers are the result of acquired genetic mutations (Figure 1-15).

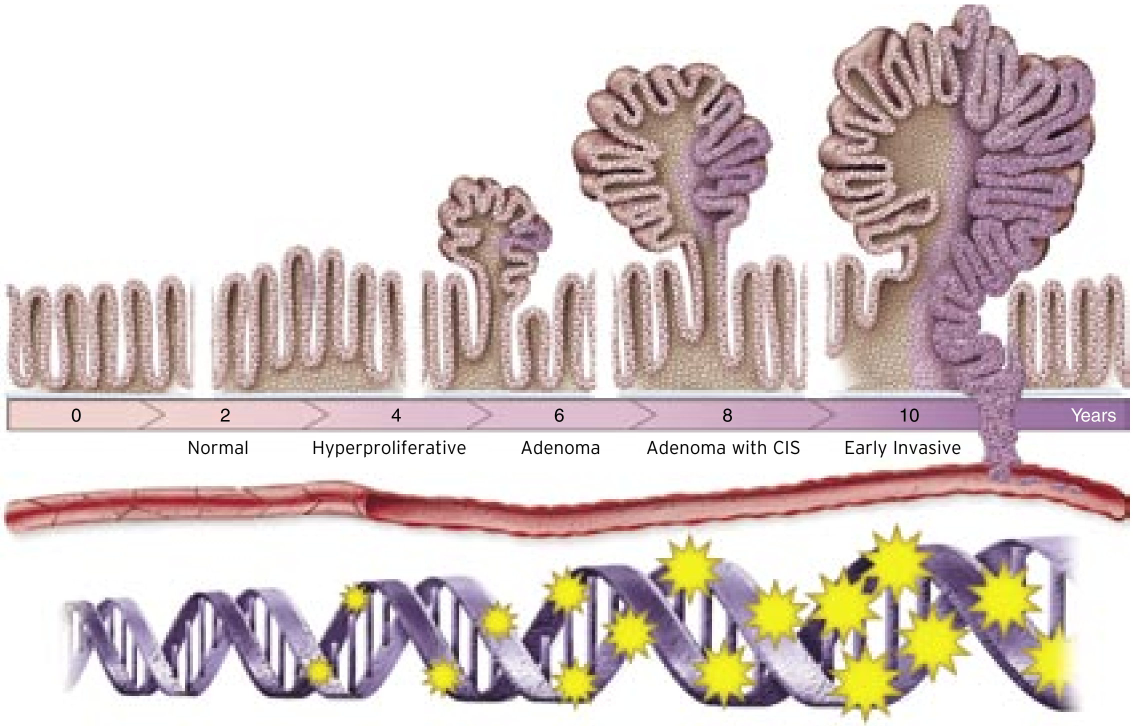

Figure 1-15 Polyp Evolution as a Series of Mutation Events

Was Doris's cancer hereditary? Neither Doris's mother, father, brother, nor sister had a history of colon or rectum cancer. She had a single benign colon polyp seen and removed at her first colonoscopy but that was more than 10 years ago. Since then, two colonoscopies had been clear. She also now understood that her age at diagnosis, more than 70 years, suggested that her risk of having a hereditary colorectal cancer was very low, a relief as she now thought about her children. So if her cancer wasn't hereditary then what caused it?

Colon cancer, like the majority of adult cancers, most often occurs in the sixth, seventh, and eighth decades of life and is predominantly the result of acquired mutations brought about by years of cellular stress and injury. The transformation to cancer is slow, taking years or decades as gene after gene is mutated until one day the mutations are extensive enough to meet the criteria that define cancer. The most serious mutations are those that confer on a cell the behaviors of invading surrounding structures and spreading through the BLOOD and LYMPH circulations. This was my next topic to discuss with Doris and Sam.

Invasion and Metastases

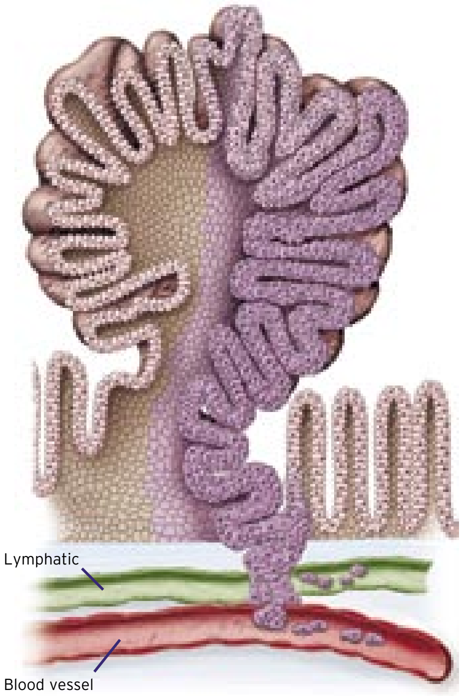

Figure 1-16: Vascular and Lymphatic Invasion

Doris's normal colon exam just a little more than four years ago, the recent onset of rectal bleeding, and the fact that she felt perfectly well caused her to be optimistic that her cancer was found early, before it was invasive. Unfortunately, the biopsy revealed an area of invasive cancer cells (Figure 1-16). What makes invasive colon cancer more problematic is the possibility of cancer cells entering into the blood. As I explained earlier, the colon, and the layers of tissue that comprise it, is a living organ composed of cells. Every cell must have a blood supply to survive. Therefore, supporting the mucosal tissue are blood vessels sending off small branches that not only nourish each of the living cells that make up the mucosal layer but also retrieve the water reclaimed by the crypt cells. As the invasive cancer grows through or infiltrates the layers beneath the mucosa, root-like projections of tumor may also grow through or infiltrate the wall of nearby blood vessels. Once exposed to the bloodstream, cancer cells may break free from the growing cluster (tumor) gaining access to the blood circulation as it flows through the colon (Figure 1-17).

If individual cancer cells or cell clusters survive in the blood circulation, they may adhere to or anchor to the wall of a blood vessel anywhere in the body and there begin a new nest of growing cancer cells. This nest may then invade through the blood vessel wall (just as it originally invaded through the mucosa). The nest may then extend into the organ in which that blood vessel is located (the lung, the liver, etc.), forming a cancerous tumor in that organ (Figure 1-18). The nest of colon cancer cells anchored into a blood vessel of another organ where it then forms a cancerous tumor is what doctors call a METASTASIS (a similar process can occur within the lymph circulation of the colon, as explained in Chapter 3).

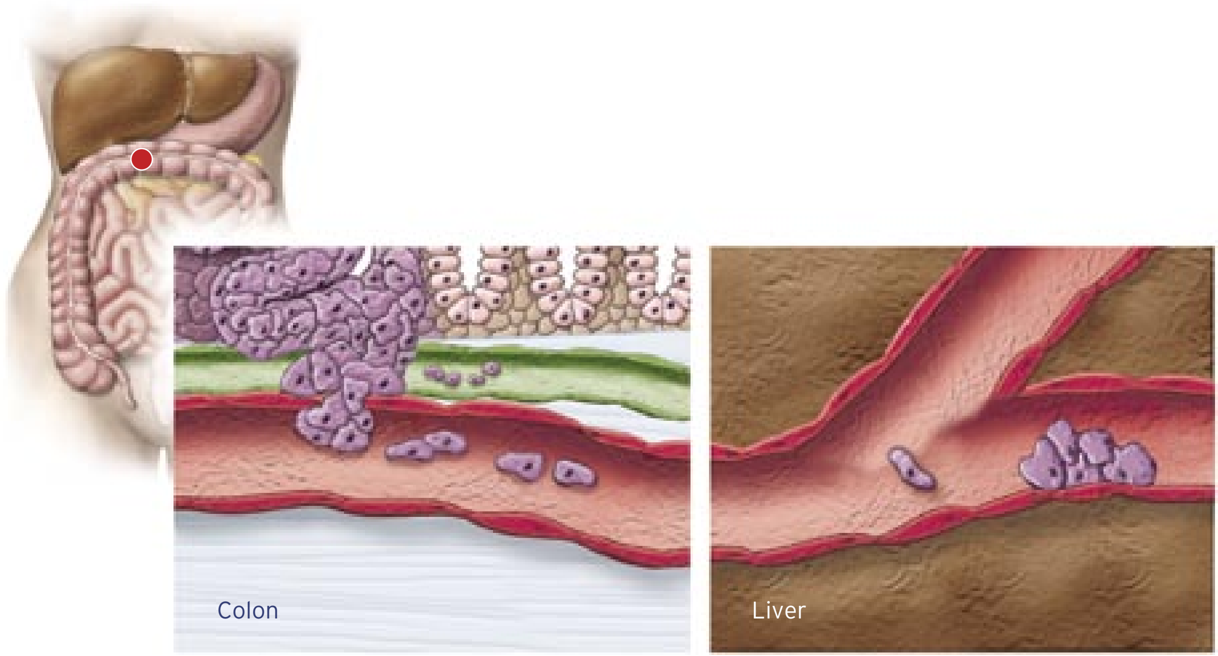

Figure 1-17: Downstream Adherence and Nesting of CirculatingTumor Cells

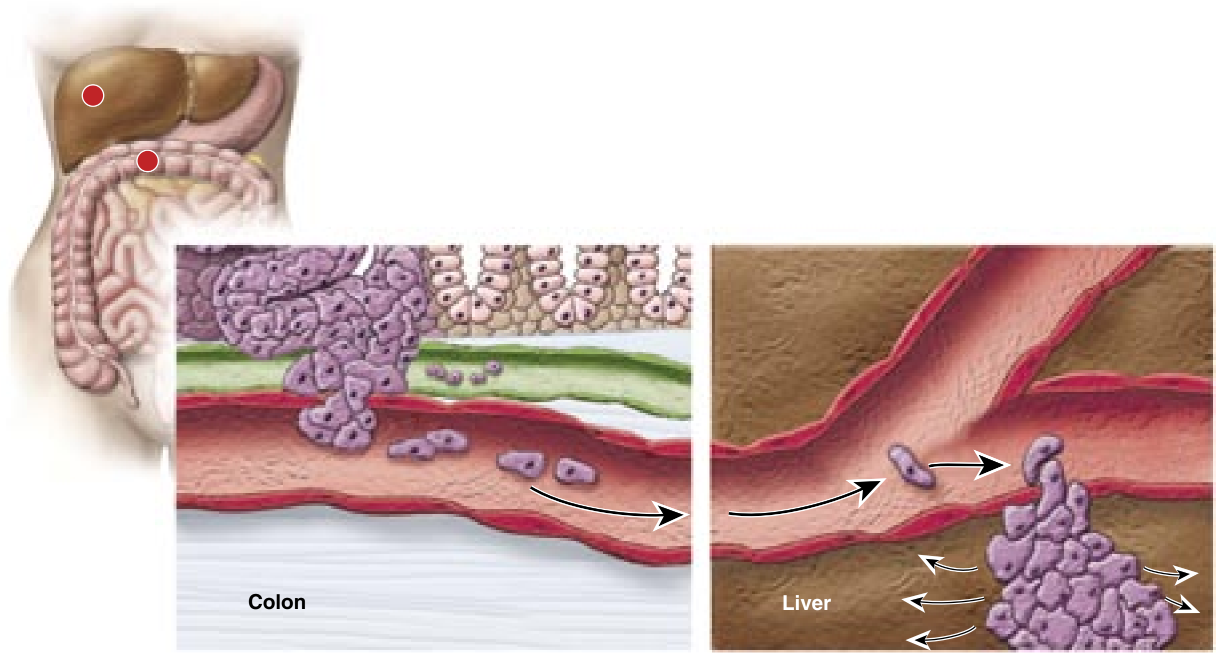

Figure 1-18: Metastatic Tumor Formation in Liver

The overriding concern for the patients with infiltrating or invasive colon cancer, and the doctors who treat them, is whether colon cancer cells have escaped into the circulation and might develop into metastases. The mission of the medical oncologist, like me, is to determine the risk of metastases in order to either do something preemptively to destroy the escaping cells before they anchor, nest, and/or invade another organ (ADJUVANT THERAPY) or to treat the metastases if they can be identified or are readily apparent (METASTATIC THERAPY).

Fortunately for Doris, like most men and women who undergo regular colon cancer screening, if a cancer is diagnosed, even when that cancer is invasive, it is found in its early stages when cure is likely. *Three facts about colon cancer are worth enumerating here. Fact one, 90% of all colon cancers found during routine screening colonoscopies are cured. Fact two, 90% of colon cancers arise from acquired genetic mutations and occur in people over the age of 50, the age at which routine screening-colonoscopies should commence. Fact three, more than 80% of all colon cancers could be prevented or cured if all at risk individuals, which means everyone upon turning 50, underwent screening. The simple math is overwhelming. If routine colon cancer screening guidelines were followed, more than 80% of colon cancer deaths would be avoided.*

Unfortunately, some colon cancers, about 10%, arise in men and women under age 50 who have no known risk of hereditary colon cancer. Eric was such a patient. Let's move on to the next chapter as I introduce Eric. We will discuss the second most common presenting SYMPTOM of colon cancer, IRON DEFICIENCY ANEMIA, and the bleeding colonic tumors that are responsible. We'll catch up with Doris and Sam a bit later.