ADVANCES IN INFLAMMATORY BOWEL DISEASE 2004

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Determining the correct diagnostic tests and selecting appropriate medications are only the initial steps to living and coping with Crohn’s disease or ulcerative colitis. Education and understanding as much as you can about these diseases is critical to becoming a strong advocate for yourself so you may maintain the quality of life you deserve. Learning:

• What is known about the cause of these diseases?
• What to expect?
• How they affect your body?
• What you can do to improve your health?
• What medications are available to help?
• What are their risks and benefits?
• What is known about nutrition in these diseases?
• What new medications are being studied?
• What questions are being asked in current research?

The answers to these questions, and many more, are important for you to know in order to take back control of your life from these diseases. Learning as much as you can affords you the best opportunity to maintain yourself in the
Our current medical system can occasionally render patients, and their families, very passive or remotely involved in their own care. A visit to the doctor can result in an order for a set of tests and a list of medications, but not enough time for interaction, questions, answers and education.

This set of slides aims to fill in the educational gap to help you, your family and friends understand these diseases. The slides have been carefully assembled by a team of health providers and educators in order to provide a broad overview of these diseases, what causes them, how they are investigated and treated.

One company’s motto is “an educated consumer is our best customer.” This motto rings true in healthcare, particularly for a chronic illness that alters your life in so many ways. This slide set is part of a broader program that you might set out for yourself to:

• Become a strong advocate for your own health
• Be actively involved in limiting the disease’s impact on your life
• Lead your life the way you choose.
Inflammatory Bowel Disease (IBD) vs. Irritable Bowel Syndrome (IBS)

- IBD = *Inflammatory Bowel Disease*
  - Chronic intestinal *inflammation*
  - Crohn’s disease, Ulcerative Colitis
- IBS = *Irritable Bowel Syndrome*
  - No tissue abnormality
  - Change in bowel habits
    - Diarrhea/ Constipation/ Alternating bowel patterns
  - Pain relieved with bowel movement
  - Increased sensitivity to intestinal motility

**IBD**, or *Inflammatory Bowel Disease*, encompasses two broad diseases: ulcerative colitis and Crohn’s disease. IBD, as the name suggests, is a disease in which some part of the bowel (esophagus, stomach, small intestines and the colon) is inflamed.

**IBS**, or *Irritable Bowel Syndrome*, differs from IBD by much more than a single letter. A different and very common disorder, IBS is a defined set of symptoms in which there is, typically, a change of bowel habits, with abdominal pain or cramping relieved with a bowel movement. IBS-related complaints or symptoms vary greatly between individuals and can include diarrhea, abdominal cramping, bloating and/or constipation. IBS is the accurate diagnosis when a patient presents with abdominal complaints but does not, on examination, have inflammation of the intestines.

Symptoms for IBS and IBD can be similar, at times making the diagnosis difficult. In addition, occasionally a patient may have both IBS and IBD, complicating an already difficult situation. However, the treatments for IBS and IBD are not similar. They are different diseases. These slides focus only on IBD - Inflammatory Bowel Disease.
Inflammatory bowel disease (IBD) is a fairly common condition. It is estimated that more than one million people in the United States have IBD. The number of IBD patients is split equally between those with Crohn’s disease (CD) and those with ulcerative colitis (UC).

The incidence of UC has remained steady (2 to 6 per 100,000), whereas the incidence of CD has been increasing. About one-third of cases present in the second decade of life, with the peak incidence between 10 and 30 years of age, although very young children (2% of cases) do occasionally develop IBD. Studies also show an increased incidence in the elderly between the 6th and 7th decade. Women appear just slightly more likely to develop Crohn’s than men; some studies suggest men develop UC at slightly higher rates than women.

However, these estimates are based on studies in selected communities and may not be representative of the occurrence of IBD in the country as a whole. One part of a bill before Congress concerning IBD would be to prepare a large national survey to determine an accurate number of people in the U.S. with these diseases.
IBD patients account for nearly three-quarters of a million physician visits per year and are often hospitalized. CD accounts for approximately two-thirds of these visits/hospitalizations (there are an estimated 20,000 hospitalizations and 250,000 physician visits for UC yearly), although these figures may change as use of outpatient treatment becomes more sophisticated with the more frequent use of such interventions as intravenous medications.

Most of the hospitalizations for IBD involve surgery. Only 20% of UC patients in the United States undergo surgery; 50% to 80% of CD patients will eventually require surgery to repair some complication, such as obstruction, hemorrhage, fistulization or refractory disease.

These conditions usually occur in discrete flares with periods of quiescence. In as much as these diseases cannot be cured, they are best managed with a maintenance strategy to minimize symptoms, prevent complications and avoid premature mortality.
IBD includes ulcerative colitis and Crohn’s disease, two different and distinct diseases. There are people with definite Crohn’s disease and others with definite ulcerative. However, occasionally (as often as 5-15% of the time) a thorough medical evaluation still does not indicate a clear diagnosis. Those in whom a diagnosis is uncertain or cannot be determined are considered to have “indeterminate colitis.” Occasionally, even when a diagnosis appears definite, the final diagnosis can change.

While it may, on occasion, be unclear which disease a patient has, one cannot have both diseases. Several slides in this presentation will demonstrate those features that help indicate the difference between the diseases. Some of the treatments are the same but others are more specific to one particular disease.
The frequency with which these diseases occur in different parts of the world may offer intriguing clues to their cause. These diseases have been observed in their greatest numbers in the “industrialized world,” predominantly North America and Europe (interestingly with more in the north than south) and, to a lesser extent, in Australia and Japan.

Countries in the so-called developing world, such as India and China, appear to have a very low number of cases of these diseases, though careful studies are unavailable and whether this reflects inadequate recognition or other differences is not certain. Interestingly, some reports from China and India suggest a significant increase in recent years and, therefore, are no longer considered rare diseases. This perceived increase in people with IBD in the developing world may represent improved diagnosis or access to certain diagnostic studies, but physicians in those countries feel the increase represents a genuine increase in the number of patients with these diseases.

Why IBD is more common in the industrialized world is unknown. Factors suggested as responsible include the relative cleanliness of the industrialized world, dietary changes, use of antibiotics, smoking and stress. However, none of these have been well researched or clearly established.
The current understanding of both Crohn’s disease and ulcerative colitis identifies three factors which interact to cause the development of these diseases in an individual: genetics, environmental risks and an abnormality of the immune system. Any one of these factors, by itself, is insufficient to develop the disease.

For example, smoking is a risk factor for the development of Crohn’s. However, many people smoke and do not develop Crohn’s. But for those with a particular genetic predisposition or other immune abnormality, smoking can be a particularly critical influence that affects the development or severity of Crohn’s disease.

Research is rapidly increasing our understanding of the specific details for each of these areas which contribute to the development of IBD, though much remains undetected. A number of environmental factors have been identified, but others remain unknown. One gene in which a defect is a known risk for Crohn’s disease has been identified. An intensive search continues for others.
Genetics, Environment and the Immune System contribute differently in each patient. The part each plays and the nature of its influence is a determining factor for the disease:

- What type of disease develops
- How severe it is
- How extensive it is
- To what medications it responds

The strength of a particular factor, such as genetics, likely determines whether a patient develops IBD and the nature of their disease:

- Mild or severe disease
- Small bowel Crohn’s versus colonic disease
- Complications such as perforations, strictures etc.

In some individuals, genetics is clearly a very strong factor with numerous members within a family developing Crohn’s or ulcerative colitis. In others, genetics likely plays a relatively minor part and the environment is likely a much more powerful determinant. As we are just beginning to have better insights into the genetic and environmental aspects, the conception of these diseases is being continually refined.
Several lines of evidence show that genetic factors contribute to the development of IBD. Racial and ethnic grouping of IBD is one line of evidence. A 3- to 4-fold increase in the risk for IBD has been identified in the Ashkenazim (Jews with eastern European ancestors) than in their non-Jewish neighbors. But we need to be cautious about concluding too much from these studies. It used to be thought that African-Americans rarely developed IBD. However, this thinking has proven to be incorrect and environmental factors, rather than genetics, may have been more responsible for these perceived differences.

The occurrence of IBD in one patient in a family, increases the likelihood that the patient’s brothers or sisters may develop the disease compared to those without any family member involved. The risk is increased by 30 times among siblings of an individual with Crohn’s, compared to those without Crohn’s. Siblings of a patient with ulcerative colitis have a 10 to 20 times increased risk for ulcerative colitis. Lastly, a substantially higher occurrence of IBD in identical twins than in fraternal twins suggests that genetic factors are involved as well.
To explain one study in further detail: a sizeable group of twins were studied in which at least one of the twins had either ulcerative colitis or Crohn’s disease. Some of the twins were identical twins (the two individuals have the exact same genes) and some fraternal twins (they are not identical and share about 50% of the same genes). The difference in the genetic sharing in the two types of twins allows us to study the risk of developing IBD in two individuals with identical genes compared to two others who share only 50% of their genes (similar to brothers and sisters who have the same parents).

This study helps to understand the role genetics plays in the development of IBD. Information was gathered about each patient in the twin pair. Among identical twins in which one had Crohn’s, the risk for the other twin developing Crohn’s was a bit more than 50% (58%). This differs dramatically from the risk to the other fraternal twin whose twin has Crohn’s (about 5%). Furthermore, if one of the identical twins has ulcerative colitis, the likelihood of the other identical twin developing ulcerative colitis is about 5% compared to a minimal risk for a fraternal twin whose twin has ulcerative colitis.
This study suggests that there is an important genetic factor in both of these diseases and that the genetic link may be stronger in Crohn’s disease than in ulcerative colitis. However, it is important to point out that even in identical twins, while about 50% develop Crohn’s if their twin has Crohn’s, about 50% will not. This fact also suggests that while genetics is very important, it is not the only determining influence, as not all identical twins develop Crohn’s if their identical twin does. The environment plays an important part as well, whether to induce the disease or protect against its development.

<table>
<thead>
<tr>
<th>Disease Presence in Twins</th>
<th>Identical twins (%)</th>
<th>Fraternal twins (%)</th>
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<tbody>
<tr>
<td>UC</td>
<td>6.3</td>
<td>0</td>
</tr>
<tr>
<td>CD</td>
<td>58</td>
<td>3.9</td>
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Genes provide the code of instructions, which determine the building blocks for all of the 30,000 or more proteins that make up our bodies. A defect in a specific gene causes the body to make a protein that does not function appropriately. This type of genetic defect can lead to many diseases, such as in hemophilia, sickle cell disease or cystic fibrosis. These are examples of a single gene defect that leads to a particular disease.

Crohn’s disease and ulcerative colitis have important genetic factors, but there is not a simple or single gene defect leading to the disease. Furthermore, these diseases are not uniform. There can be several different pathways, several different abnormalities, which can lead to a similar end result. Several different genes are likely involved. Therefore, these diseases are more complex and result from a gene or set of genes and a complicated interaction with the environment. It may not be one gene that provokes the disease but several or numerous genes may be required for some individuals.

Searching for IBD Genes

• Candidate Gene Approach
  – Based on “hunch”
  – Investment low, likelihood of success low

• Genome Wide Screen
  – Better in families with multiply members affected
  – Looking for evidence of “linkage”
In order to identify a gene that may be responsible, researchers begin with a large number of samples of blood from people with IBD, as well as samples from relatives without the disease. The DNA (the code for the genes) is extracted and a search can be done in a variety of ways. A researcher might have an idea for a “candidate gene” (an educated guess based on what is known about the gene) and conjecture about the disease process.

The genes can then be “sequenced” to determine if the DNA of the gene of an IBD patient varies from the gene in people without the disease. Another method of gene searching is more laborious and time consuming. It involves “mapping” all the chromosomes (the entire collection of genes in a cell) to identify which segments tend to be inherited more commonly in people with IBD, and then searching more intensively near those areas to try to find abnormal genes.

These methods were employed separately by different teams to identify the first genetic defect associated with Crohn’s disease. A number of other broad areas on additional chromosomes have been determined but specific gene defects at those sites have not yet been identified.
The first genetic defect associated with IBD is in a gene called NOD2. This finding represents an enormous breakthrough in this field of research. The gene’s function, when normal, is to alert the cell that bacteria have broken into it, prompting the cell to produce an inflammatory response to try to rid itself of the bacteria. Patients with a defect in the gene do not generate as much of an inflammatory response and cannot rid the cell of bacteria. As Crohn’s disease appears to be an excessive inflammatory response and this genetic defect causes a deficient inflammatory response, how this defect leads to Crohn’s disease and its manifestations is not yet fully understood. This discovery has stimulated a great deal of research to understand how the immune system protects against bacteria.

The identification of this gene is critically important but the enthusiasm of its discovery should be tempered with the understanding that it does not translate into a quick cure. First we must discover the normal function of the protein for which this gene codes. That understanding should provide insight into the process, which causes the disease. Once we understand the process which leads to these diseases, we can develop ideal therapies. In addition, scientists recognize that NOD2 is only one of a number of genes which are linked to IBD and which will increase our understanding of Crohn’s and UC.
About one-third of individuals with Crohn’s disease have at least one copy of the mutated NOD2 gene. This means that over two-thirds of patients with Crohn’s have normal NOD2 genes. In addition, this gene is not associated with ulcerative colitis. Each cell contains two copies of each gene. Those who have one copy of the gene have a 1.5 to 4 times the risk of having Crohn’s as the general population.

The risk in the background population of developing Crohn’s disease is, at most, 1 in about 500 people. Individuals who inherit two copies of a defect in the NOD2 gene do have a risk 15-40 times that of the background population. About 3-5% of the general population in the United States carry at least one NOD2 gene with a defect, though the genetic defect is rare among African-Americans and Asian-Americans. An estimated 8 to 14 million people in the U.S. carry one defective NOD2 gene but the total population of Crohn’s in the U.S. is estimated at about 500,000. Having the genetic defect in NOD2 does not mean that that individual will definitely develop the disease. So whereas genetics is very important in developing IBD, the environment plays a crucial role as well.

### Significance of NOD2 Risk to Developing Crohn’s disease

- **One copy of Mutated Gene**
  - 1.5-4.0 fold risk
- **Two Copies: 15-40 fold risk**
  - 10% of CD patients carry two copies
  - 28% of CD patients carry one copy
  - Actual disease presence with one or two gene copies is less than 10%
Environmental triggers that combine with the genetic predisposition to provoke the development of IBD are being increasingly clarified, though much remains unclear. In some individuals, infections appear to play a role in initiating the disease. It is not difficult to imagine the following scenario. A group of travelers visit a tropical island, all develop diarrhea, and subsequently, all recover but one. That patient’s physician tries a round or two of antibiotics before investigating further and the patient is eventually diagnosed with colitis. Why or how that acute infection prompted a chronic colitis is uncertain.

Non-steroidal anti-inflammatory drugs (known as NSAIDs which include medications such as ibuprofen, Advil, Motrin, naprosyn, Aleve, Celebrex and Vioxx) can initiate a flare. Some patients with IBD may tolerate these medications, but it is not that one takes an Advil today and feels ill tomorrow. Instead, it is one factor among many and sorting it out can be difficult. In addition, whether these medications play a role in initiating the development of IBD is also unclear. More likely, or at very least, they might cause a flare of already established disease.
Diet may play an important role as a risk factor for IBD, but much work remains to understand this area better.

All illnesses are blamed on stress and most IBD patients will feel certain that a particular flare can often be connected to some stressful event in their life. This factor has been hard to establish in medical studies, because stress is an individual, subjective assessment and is difficult to measure accurately. Certainly, patients should not feel, as well-meaning friends or family sometimes erroneously suggest, that if they could handle stress more effectively, their disease would resolve. While there is an important connection between the brain and the body, how this relates to IBD requires further study.

Smoking is the best established risk factor in IBD, but is particularly curious as it has opposite effects in Crohn’s disease and UC.
Smoking has a surprising relationship to Crohn’s and UC, particularly because the effect in UC is opposite to that of Crohn’s disease. In Crohn’s disease, smoking is a risk for:

- Developing the disease
- More severe disease
- Greater need for more potent immune suppressants
- Rapid recurrence of disease after surgery

Furthermore, stopping smoking can lessen the disease activity in Crohn’s disease.

However, smoking, as terrible as it is otherwise, can protect against the development of UC. Nicotine patches have been shown to be of modest benefit in treating the symptoms of UC. Further confusing is the fact that not only is smoking protective of the development of UC, but a former smoker has a higher risk of developing the disease than if he or she had never smoked. Physicians who take care of many patients with UC will hear a not uncommon story of a patient who decided to stop smoking and then sometime later, developed UC. While it may seem a cruel irony, given all its detrimental effects, smoking does have a benefit in UC. Studies are underway testing a nicotine enema for ulcerative colitis.

The reasons for tobacco’s opposing effects in UC and Crohn’s are not understood. Still, the benefit it may have in UC is far outweighed by the harm it brings otherwise. While most physicians would not suggest stopping during a flare of UC, overall, discontinuing tobacco use is still advised for patients with UC and most strenuously insisted on for patients with Crohn’s disease.
We have outlined the risk factors for developing these diseases, but the question remains incompletely answered: What causes IBD? What are the actual steps involved that lead to IBD? We have clearer answers than we had several years back, and our understanding continues to evolve.

The most widely accepted current supposition is that IBD results from an abnormally regulated immune system. The colon, which is continuously confronted with an intense concentration of bacteria, has a finely tuned immune system prepared to repel any potential bacterial threat to the body, resting in a balance between factors, which increase inflammation, and those, which limit inflammation. The colon, even in its healthy normal state, leans slightly towards a state of mild, low level, controlled inflammation. This normally well-controlled condition goes haywire in IBD.

An infection, which provokes an inflammatory state in people with and without IBD may cause every individual to have temporary colonic inflammation and stir up symptoms of abdominal pain and diarrhea. Following the acute infection, most individuals reset their immune system and return to the previous state of controlled, low level inflammation. In those with UC or Crohn’s, the immune system fails to reset itself and the colon does not return to its previous healthy state. Instead there is a chronic inflammatory state, with a persistent imbalance between the forces which increase the body’s immune response and those that limit it.
We will leave the discussion of the theory of what causes IBD and leap into the "guts" of the problem, focusing on practical issues of:

- How IBD is diagnosed
- What the symptoms of IBD are
- What happens inside and outside the intestines
- How these diseases can be treated

No one test alone clearly forms a diagnosis of Crohn’s or UC. Instead, a variety of approaches and studies are necessary to get a complete picture. Needless to say, the first step to diagnose and determine appropriate therapy for any disease is for competent medical personnel to learn the patient’s medical history in detail. In seeking a health care provider, even if it is the first time, it is worth taking time to consider some important details to be able to explain them clearly:

- When did your symptoms begin?
- How severe are they?
- What are you feeling?
- Where on your body do you feel it?
- Is there a relationship between eating and your symptoms?
- What makes them better or worse?
The details of your health history serve as an important guide as to which tests may be indicated, what might be possible diagnoses and appropriate treatments. Often it is worthwhile to write things down to remind yourself of how you have been feeling and the questions which you wish to bring to the physician’s attention. The physical exam will guide the outcome. During an exam, a healthcare provider will look for any signs or manifestations of IBD (mouth ulcers, rashes, abdominal discomfort at pressure, masses in the abdomen and perianal disease).
Inspection of the lining of the intestines with colonoscopy or endoscopy is something about which many of you are knowledgeable. The scopes can look throughout the colon and the last part of the small bowel (known as the terminal ileum), other procedures can look at the esophagus (swallowing tube) stomach, the duodenum (the first part of the small bowel) and just beyond the duodenum.

Capsule endoscopy (swallowing a pill with a camera in it that transmits pictures by radio waves to a receiver worn in a belt) permits most of the small bowel to be inspected. This capsule endoscopy is not a yet a fully acceptable method to evaluate the esophagus and stomach. It is also not useful in looking at the colon. In addition, biopsies or tissue sampling cannot be performed with the capsule. Consequently, despite the wish of many people, the capsule is not a substitute for endoscopy or colonoscopy. These tests can often help in the diagnosis of UC or Crohn’s, provide a decent understanding of where the disease is active, screen for colon cancer and help guide therapy. However, they only see what is inside the intestine and do not always allow the assessment of a narrowed area or beyond a tight narrowing.

A variety of radiologic tests can help us see more completely and assess what is outside or around the intestines. These will more effectively guide the diagnosis and therapy.
Colonoscopy is a major tool to diagnose, guide therapy and monitor patients with IBD. Colonoscopy allows the lining of the colon to be visually well inspected, and also permits biopsies to be taken to assess inflammation, other abnormal areas and screen for colon cancer. The colonoscope is slightly over five feet long and can be safely inserted along the colon and into the last part of the small bowel (the terminal ileum), which is a particularly important area to inspect. More than 70 percent of patients with Crohn’s will have some inflammation in this area.

A colonoscopy can be useful as a diagnostic tool in a variety of ways. This test can assess the appearance of the colon, which will permit the colonoscopist to distinguish between Crohn’s disease and ulcerative colitis. There is a separate channel in the scope to which a long wire with a small device is attached to take biopsies.

Biopsies are samples of tissue from the lining of the colon that are about the size of the writing tip of a pen. The biopsies can help distinguish Crohn’s from UC. In addition, biopsies can be helpful to determine the severity of inflammation. The lining of the colon may appear minimally inflamed or even normal and the biopsy will determine if inflammation is significant. This can be helpful to guide the choice of appropriate therapy.

Colonoscopy in IBD

- Diagnosis of IBD (UC vs. CD)
  - Allows visualization of large intestine and ileum
  - Allows biopsies to examine colon tissue
- Determines activity of disease
- Important for pre-cancer surveillance in UC and CD
Individuals with long-standing ulcerative colitis and Crohn’s colitis are at an increased risk for colon cancer. In patients without IBD, colon cancer will usually develop in a polyp, a visibly obvious lump of abnormal tissue attached to the colon lining. In UC and Crohn’s, cancers can develop in flat areas that are not obvious by simply looking at the intestinal wall. By performing colonoscopies at set intervals in patients with longer-standing UC and Crohn’s (discussed in more detail later) and taking numerous biopsies (standardly over 34 samples), these abnormal areas called dysplasia, can be detected earlier, before development of full-blown colon cancer.
Colonoscopy is not intended to be torture, though some dread it as if it was. It should be a painless procedure. The general consensus is that the worst part is not the procedure itself (the anesthesia should eliminate discomfort), but the preparation prior to the colonoscopy, cleansing the entire bowel. A variety of methods have been developed to clean out the colon so that it will be totally emptied and will permit good visualization. Many are no doubt familiar with Golytely, a not so aptly named gallon of liquid that must be swallowed within about three hours. Even with some of the newer flavorings, few people are enthusiastic about repeating it. A Fleet’s phospho soda oral prep is a smaller volume of liquid and more rapid but can be harsher, and difficult for some patients to tolerate. A newer option is called Visicol, a preparation that involves swallowing pills.
Before we go into the details about how UC and Crohn’s disease affect the colon, we should define our terms. The gastrointestinal (GI) tract means essentially everything in the long winding tube which leads from the mouth to the anus. After food is swallowed, it makes its voyage through the GI tract by being propelled into the esophagus, which is a muscular, tube about 10-12 inches in length that empties into the stomach. The stomach, also about 10 inches in length, functions as an important reservoir, slowly releasing food into the small bowel where it is digested. The stomach, when full, can hold between 2-4 liters (a half to one gallon) of food and liquid, though some of us are capable of holding more.

The small bowel, also referred to as the small intestine, is a long tube about 1.5 inches in diameter and remarkably long, about 20 feet from beginning to end, not including about 5 feet of colon. The stomach leads into the first part of the small intestines called the duodenum, which is usually about 12 inches long. The liver and pancreas empty their contents into this area. The duodenum then leads to the first major part of the small bowel called the jejunum and the further half, called the ileum. Most of the nutritional content of food is absorbed by the small bowel, which has numerous small folds to increase its surface area and permit efficient absorption of the food. The total surface area of the small intestine, with its numerous small folds has been estimated to be the size of a tennis court.
A valve (called the ileocecal valve, which your doctor might refer to as the I-C valve,) separates the small intestines from the colon. It opens to allow whatever has not been digested and absorbed in the small intestine to pass into the colon where some of it can be broken down further by the colonic bacteria. The colon absorbs a tiny percent of nutrition, but is extremely efficient at absorbing water. When healthy, about 1-2 liters of fluid passes through the ileocecal valve and the colon absorbs more than 90% of it. If the colon is unable to absorb much of that fluid or if it is overwhelmed by the amount of fluid passing into the colon, the result is increased water in the stool, which is diarrhea.
With that as background, we will review the clinical features of ulcerative colitis. About 500,000 to 600,000 people in the U.S. have UC. Typically, UC will begin between the ages of 15-35 but can occur at any age, occasionally before the age of 5 and even after the age of 85. As mentioned previously, cigarette smoking can decrease the risk of developing ulcerative colitis. Another interesting influence, also protective against the development of UC is an appendectomy. Patients who have had an appendectomy before the age of 21, because of an inflammatory problem, (such as appendicitis) have as much as a 60% lower incidence to develop ulcerative colitis. Why an appendectomy is protective, is not known. It does not, however, protect against the development of Crohn’s disease.
Ulcerative colitis only affects the colon. The small bowel is not involved in UC. Inflammation in the colon ("itis" means inflammation) is found only superficially in the lining of the colon, but not through the whole wall, as occurs in Crohn's disease. The extent of inflammation varies in each individual. In some it may involve just the rectum (proctitis), the left side (of variable extent), or the entire colon (pan-colitis). We group all of these different subtypes together under the umbrella of ulcerative colitis but it could be refined as ulcerative proctitis, proctosigmoiditis (much of the left side) or pancolitis.

While the extent may vary, it always initially appears in the rectum and works its way up. The inflammation is always confluent or continuous from the rectum to whatever portion of the colon is inflamed. If left-sided, the inflammation stretches from the rectum throughout the left side of the colon with no normal areas within the inflamed area. Over two-thirds of patients will have inflammation just on the left side at the onset of their UC. However, as often as half of the time, inflammation can progress to involve the entire colon.
The clinical problems caused by UC vary in each patient, but tend to be more similar than in Crohn’s. While the symptoms differ to some degree depending on how much of the colon is inflamed, bloody diarrhea tends to be the most consistent problem. Abdominal cramping can be quite common as well, particularly at the time of a bowel movement. While some patients with UC suffer from more persistent pain, generally, that is not the rule. However, pain is often noted with severe flares. Frequent, small stools accompanied by a persistent sense of having to evacuate and a great sense of urgency, is often felt with more significant rectal inflammation. Other symptoms such as fatigue, low energy and feeling rundown are not specific to UC but will often accompany colitis. Fever, (particularly low-grade, below 101) can be caused by UC. If a patient has a temperature greater than 102 degrees, an additional cause such as an infection should be investigated.

UC can also cause symptoms that are outside the bowel (known as systemic or extra-intestinal manifestations). Joint pains, particularly in the larger joints; hips, knees, can occur in more than 40% of patients, as well as inflammation in the eye and skin.
The name “ulcerative colitis” suggests that the lining of the colon is covered with ulcers, but ulcers are typically seen only in severe colitis. The normal lining of the colon or mucosa is slightly pink in appearance, like the inside of the lining of your cheek, with a delicate lace-like pattern of small blood vessels. Small ridges or folds are also spaced throughout the colon. The lining of the colon in mild ulcerative colitis is redder than normal (erythematous) without the delicate pattern of blood vessels. This indicates inflammation is present in the tissue. The lining can also be “friable,” meaning that the surface can bleed or ooze a small amount of blood when stroked gently with a cotton swab. This common abnormality seen in UC can explain why some patients may observe some bleeding or even severe bleeding as their stools become more formed, which causes them to rub more firmly against the lining of the colon.

Sometimes inflammation can be present with little or no redness or other abnormalities seen. Examination of biopsies under the microscope can be a more definitive indication of what is happening in the lining of the intestine. In more severe colitis, the colon may have ulcerations, may be swollen (edematous) and the surface may be covered with thick substance, a combination of mucous and pus, that drips off of the inflamed surface (called an exudate). In long standing severe colitis the colon begins to loose its ridges and other features (sometimes called featureless or having a lead-pipe appearance).
Patients with UC can develop a number of problems, which occur because of chronic inflammation in the colon. The greatest concern is cancer, which will be dealt with in detail in later slides. Other complications can be devastating but, fortunately, are rare. Bleeding usually is mild, though it might look frightening: it takes only a few drops of fresh blood to turn a toilet bowl red. However, on occasion, bleeding can be much more dramatic. In addition to a large amount of bright red blood (enough to fill at least a large glass), symptoms include dizziness, in any position, lying down or standing up. This would indicate that you might have rapidly lost a large amount of blood volume, which is distinctly different from when you loose a small amount, which is common in UC. (However, you can have similar symptoms from dehydration as might happen with severe diarrhea.) If you were bleeding much more dramatically than usual, an urgent call to your physician would be essential. This type of devastating bleeding fortunately happens to only a few patients with UC.

A second problem which can also cause an acute, urgent crisis is when the inflammation erodes through the colon and creates a hole (perforation), during which the contents of the colon to spill into the belly, which is normally clean and sterile (without any bacteria). This would cause sudden, severe pain, high fever and overwhelming infection. Although, rare, this set of symptoms is not subtle and would be a clear indication to contact your physician immediately or to go directly to the emergency room.
A stricture, or a scarred down, narrowing in the intestine, is something that is less common in UC than Crohn’s. When it occurs in UC, a stricture can be of particular concern as a manifestation of a developing cancer at the site. Biopsies should be taken at that spot to rule out colon cancer. A stricture in Crohn’s is of less concern for cancer, but still can cause problems such as blockage of the passage of food, causing pain after eating.
Unlike UC, Crohn’s can develop anywhere in the intestine, from the mouth to the anus. However, it does not jump around. Usually when it announces itself in one or several locations, it remains there. If surgery is performed, a recurrence is usually at the original site. Most commonly Crohn’s disease occurs in the last segment of the small bowel (ileum), which is why Crohn’s is occasionally referred to as ileitis. (At one time Dr. Burrill Crohn called it “terminal ileitis” because it was first identified as occurring in the last part or “terminal” ileum. However, the use of the word “terminal” sent the wrong signals, as this is not a terminal disease. Instead, physicians referred to it as “regional ileitis”.)

About 70-80% of the time inflammation can be detected in the last part of the small bowel. The disease in the small bowel may be limited to just a few inches or can be several feet in length. The first half of the small bowel, duodenum and jejunum can be involved as much as 20%, the stomach in 5-10% and the esophagus 1-2% of patients with Crohn’s. The colon can be the primary site of involvement in about 20% of patients with Crohn’s disease. Unlike UC, where inflammation is continuous and almost always starts in the rectum, Crohn’s more often does not involve the rectum (“rectal sparing”). In addition, Crohn’s disease is not always continuous. There can be a diseased segment, followed by a healthy segment, followed by a diseased segment. This type of involvement, typical of Crohn’s, is called a “skip lesion.” Crohn’s varies a great deal among individuals and is less homogeneous than UC.
Each patient’s Crohn’s disease manifests itself differently. The symptoms are less similar than is seen with UC. A patient might have a great deal of abdominal pain, but no diarrhea; a child might not have any pain or diarrhea, just fatigue and poor growth. A patient could experience a great amount of diarrhea and nausea. The problem with which a patient suffers depends on:

- The location of the inflammation
- The length of intestine involved
- The severity of disease
- History of surgery
- Presence of strictures
- Other symptoms

Most commonly, patients with Crohn’s have diarrhea, which can vary from a few loose stools to more than 20 stools per day. However, about 10 % of patients with Crohn’s do not experience any diarrhea.
Abdominal pain and tenderness depends on the amount and location of inflammation. As Crohn's most often occurs in the right lower part of the abdomen, pain will be present usually in that same area as well. Other symptoms can be less specific in terms of location, such as loss of appetite or loss of weight.

Weight loss often occurs because patients will not eat normally. They sense it will cause more diarrhea or abdominal pain. Fever (a temperature greater than 100 degrees) can be attributed to intestinal inflammation, but we would be concerned about some other problem or complication if the temperature is greater than 101.5 or 102 degrees. Fatigue can also be a major problem, as well as an early warning of a problem brewing. Of course, numerous other problems, related or unrelated to Crohn’s can cause fatigue. Another major set of symptoms caused by Crohn’s can be fistula’s (like a straw or small pipe connecting two areas) or perianal ulcers. Fistulas can cause perianal pain, soreness and drainage of pus or stool.
The appearance of Crohn’s, when seen through a scope, can have several features which are characteristic of Crohn’s. However, it may also look like UC, so much so that it can be impossible in some cases to distinguish the two diseases endoscopically. The classic appearance of Crohn’s includes definite ulcerations with normal, healthy-appearing intestinal lining in the surrounding tissue. Typically there are long, linear ulcerations (sometimes called bear claw ulcerations because it looks as if a bear was scrounging around in the intestines scraping deeply as he moves along his way). “Cobble-stoning” is a characteristic finding, with deep ulcerations criss-crossing, leaving nubs of normal tissue (the cobblestones).

Crohn’s can also cause the development of a tight stricture, a narrowed, fibrotic area, which might not allow the scope to pass through. These strictures develop over a long period of time, usually years, and result from chronic inflammation and the body’s attempt to heal. Slow gradual scarring can continue to tighten over years. Also, as mentioned, Crohn’s can have a diseased area followed by an abrupt change to normal and then a diseased segment. Detecting a small fistula by colonoscopy can be difficult, though larger fistula can be occasionally seen. They appear through the scope as a nub of inflamed tissue and a central opening.
As in UC, Crohn’s can develop a variety of complications in the intestines including perforation, stricture or bleeding. Cancer has been emphasized as a potential complication of UC, but patients with Crohn’s colitis can have an equal risk of developing colon cancer and should undergo similar screening. Two problems, more specific to Crohn’s disease, are the development of a fistula or an abdominal abscess. As many as one-third of patients with Crohn’s will eventually develop an abscess at some point during their life.

An abscess is an infection within a closed place that, not having any point to drain, develops into a collection of pus and debris from the infection. This abscess can cause abdominal pain (often severe) and fever. The abscess in Crohn’s develops, presumably, from a deep ulceration or fissure burrowing through the wall of the intestine which causes a small perforation or opening into the abdominal cavity. This focal opening into the abdominal cavity sets up a localized infection that, in turn, develops into an abscess. Usually an abscess, unless very small, requires antibiotics, drainage and, most often, surgery to remove the perforated part. Another complication is the development of a fistula, a process and problem particular (though not unique) to Crohn’s disease.
This slide gives a view of an abdomen diseased with Crohn’s as seen through the eye of the surgeon. Unlike UC, which inflames the inner lining of the colon, Crohn’s involves the full thickness of the intestinal wall. In addition, there is a sheet of fat (the yellow substance in the slide) which lies over the intestines. In Crohn’s, fatty tissue, which hangs from one side of the intestines, can shift to encase the outer surface of the inflamed intestine, which gives a characteristic appearance, called “creeping fat.” If a small, localized infection develops into an abscess, as described previously, the appearance is often that of a localized, inflamed section adjacent to an inflamed segment of bowel. Often an abscess can attach itself to surrounding intestine.

When the surgeon opens the abdomen to operate, the intestines can sometimes be stuck together and difficult to separate, occasionally requiring a larger resection than anticipated. If a perforation is not localized, develops into an abscess or is a large perforation, peritonitis can develop. Peritonitis, in Crohn’s, usually results from a larger perforation into the abdominal cavity, outside the intestinal wall, spreading bacteria and other intestinal contents throughout the usually sterile (meaning- without any bacteria) abdomen, causing diffuse inflammation and areas of infection. This can be a very serious problem requiring hospitalization, antibiotics and surgery.
These ulcerations or fissures burrow through an intestinal wall and can lead to:

- Small, localized perforation which leads to an abscess
- Broader perforation developing into peritonitis
- Continuation through the wall that burrows into an adjacent segment of intestine, which forms a connection between the two intestinal segments called a fistula

A fistula is a tunnel or tube connecting two different intestinal segments or different organs. A fistula might develop from the intestines through to the skin (entero-cutaneous fistula meaning from the bowel to the skin) or an ileo-colonic fistula (ileum to colon) or recto-vaginal fistula (rectum into the vagina).

The pictures in the slide show what an ileo-ileal fistula (ileum to another segment of ileum) on the left. The drawing on the right shows two different types of fistulae: an ileo-colic fistula (ileum to colon) and an ileovesicular fistula (ileum to the bladder). Each can present its own set of symptoms. Some of these internal fistulae (not connecting up to the outside skin) are not problems which demand surgery or great concern (a fistula jumping from one segment of small bowel to another a few inches further down) may not cause any symptoms and can be left alone, just watched. Others can be concern of with surprising symptoms: a patient with a fistula to the bladder can have a symptom in which he or she urinates air (air from the intestines passing into the bladder).
A fistula can be internal or external, meaning connecting from an internal structure (such as the colon or ileum) to the outside surface of the body. A fistula can also develop inside the body between two other organs such as the small bowel to the bladder, the small bowel to the colon or the colon to the vagina. Most often fistulae arise from the inside surface of the anus, penetrating through layers of tissue to outside the anal area. These fistulae (plural of fistula) can have one or multiple single openings, draining pus or stool. These fistulae can also block up, stop draining and grow into a perianal abscess, causing pain and fever. A team of both gastroenterologist and surgeon together can be helpful to determine the best way to manage these problems.
A variety of problems can develop in the perianal area in patients with Crohn’s disease. Fistulas and abscesses are frequent, occurring in more than 30% of patients with Crohn’s disease. Fistulas do not occur in ulcerative colitis. Perianal fistulas result from small collections of inflammation and infection which burrow their way from right around the anal muscle or sphincter to make their way out to the skin. Sometimes these fistulas can be simple; with one opening draining, but other times they can be more complex, a complicated web of canals under the skin in the perianal area with numerous openings. Fissures are sores or ulcerations in the lining of the skin crossing the anal canal, which can be painful. Not infrequently, patients with Crohn’s can develop fleshy growths on the outside surface near the anus, which are sometimes mistaken as hemorrhoids. Usually they are not painful and cause only an occasional annoyance. They resemble and therefore are described as “elephant ears.”
While we think of UC and Crohn’s as diseases of the intestine, they can be more systemic illnesses, causing disease or problems in numerous other parts of the body. These extra-intestinal manifestations do not occur in everyone, but patients with these diseases should be aware of them. Patients should understand that these are related to their intestinal disease and should contact their health care team for early intervention.

Some of these systemic, extra-intestinal manifestations can affect as many as half of patients with IBD: They include:

• Arthritis
• Eyes:
  • Iritis; Uveitis; Episcleritis (inflammation in different parts of the eye which can cause painful red eye and feeling as if there is sand in them)
• Skin
  • Pyoderma gangrenosum (ulcerated skin usually on the front of the legs); Erythema nodosum (red, painful nodules usually on the legs)
• Kidney stones
• Gallstones
• Liver
  • More common in UC (less than 5%) than Crohn’s, inflammation in the bile ducts in the liver-primary sclerosing cholangitis
• Bones
  • Osteoporosis, or thinning of the bones, particularly associated with use of steroids
We know that these extra-intestinal manifestations are related to the intestinal disease, though we do not know why or how these problems happen to some patients and not to others.

The pain patients feel in their joints tends to be in the larger joints, such as the hips and knees. In the peripheral joints (outside the spine and sacroiliac joints), pain tends to be worse when the intestinal disease flares and better when the intestinal disease is under control. For some, the joints or other extra-intestinal manifestations can be warning signs that their Crohn’s or UC is about to flare. To bring joint pain under control, as well as many of the extra-intestinal manifestations, efforts to get the intestinal disease in remission will help the other manifestations as well.
This slide presents pictures of two of the skin problems that can develop in patients with IBD. Pyoderma gangrenosum, fortunately not a common problem, can occur anywhere on the body. They are deeply ulcerated areas of skin, often weeping a lot of pus, which typically appear on the lower and front part of the legs. Curiously, they can occur at sites of previous trauma or injury. Usually, though not always, when the intestinal disease improves, the skin will improve. A number of therapies, both topical, oral and IV medications can be very effective in treating this problem. Another skin problem, erythema nodosum, which means "red nodules," is just that, red bumps, usually quite painful, on the front of the lower legs, which often appear at the beginning of a flare. Both of these skin problems occur with other diseases but are associated with IBD as well.
The treatment of patients with UC and Crohn’s involves a great deal more than medications. While many of these slides will focus on the medications, the full care of the whole patient requires broader issues and concerns. A team of healthcare personnel is required to provide complete care for those with complex disease, with gastroenterologists, surgeons and others working closely together. In addition, nutrition is an additional important aspect. The emotional aspects of coping with these diseases, the added concerns placed on patients, the family and friends need to be dealt with directly to try to minimize the intrusion and disruption these diseases can have in patients’ lives.
This diagram presents some of the numerous and complex issues of which patients with IBD and their families should be aware in dealing with these diseases. These issues are of concern to their healthcare providers as well. As these are life-long diseases, the emphasis is ultimately to:

- Bring the disease into remission
- Maintain remission
- Deal with the variety of emotional, psychological and medical issues
- Encourage the patient to be involved.

For most with IBD, these diseases can be dealt with adequately on all levels, so that the impact on their quality of life is minimized. Even for those in long-term remission, these diseases can act up without warning. Understanding them and how they affect the patient is central to control the disease and to develop an attitude and approach, which can be helpful to lessen the problems, they can bring and leave in their wake.
The British Society of Gastroenterology Initiative developed guidelines as to the appropriate expectations that patients should be entitled. Recently, the Society published these Guidelines, which emphasize the steps that should be taken when confronted with a patient who does not yet have a firm or definite diagnosis of IBD. As such, they recommend referral from the community GP to a gastroenterologist for a thorough evaluation. They emphasize that adequate time and effort on initial discussion to explain the disease and how it should be investigated/treated is essential.
For long-term care, the British Guidelines stress many social aspects, such as prolonged, continual care by the same physician; a primary care doctor, if a capable one is available, or a specialist. They emphasize quality of life issues, patient dignity, access to second opinions or referral care, when appropriate, not just hard scientific goals (such as preventing surgery, minimizing bowel movements, and lower values of a marker of inflammation, measured by a blood test). Finally, they recognize that there will be future problems; things will not always go smoothly, and they plan to be able to handle complications and change in plans within their system.
What Patients Should Expect

• Hospital management
  – Knowledgeable MD/nursing staff
  – Willingness to refer to specialist center
  – Communication with patients/families
  – Encouragement of self-management
  – Choice in medical/surgical therapies
  – Access to dietitians, social workers

The hospital involved with the gastroenterologist must take measures to ensure that it will:

• Have the expertise and ability to handle the case
• Be prepared to offer referrals, education, nutritional and social counseling
• Be available to communicate with the patients and their families
• Co-manage the patient with the original primary care doctor, in a collaborative approach
This next section will explore, in detail, medications commonly used in the treatment of IBD. Many medications, but not all, are used to treat both diseases. Crohn’s and UC are diseases that have a broad range of severity. Some patients might have minimal disease symptoms every few years; others may have almost non-stop, severe symptoms. The general approach is to start with mild medications to treat mild disease and stronger medications, with their associated risks, reserved for more severe disease. Some use the image or model of a pyramid, starting at the bottom with more widely used therapies that are mild both in risk and benefit, working the way up to medications which are more potent but also have more significant risk of side effects.

The first class of medications are called 5-ASA agents, which have been around in one form or another for over 50 years. The first one, the mother of all 5-ASA compounds, was first developed by Dr. Nana Svartz, a woman working in Sweden, who was trying to develop the compound sulfasalazine, (trade name is Azulfidine) in order to help, if the story is true, a close friend of the king of Sweden who suffered from arthritis. A strong benefit in arthritis was shown and individuals with arthritis and colitis noted that their colitis improved as well. While we were still not sure how this compound worked, it became a pillar of therapy, particularly for UC, as well as Crohn’s in the colon. The other 5-ASA compounds have been derived from it. The active ingredient in these medications are all the same. They differ in the way they are delivered in the body and where in the digestive system they are released.
Two other broad categories of medications used in IBD include antibiotics, which are used primarily for Crohn’s. The ones used most often include Cipro (generic name is ciprofloxacin) and Flagyl (generic name is metronidazole). There is little evidence that antibiotics are effective for UC, but they are used widely in Crohn’s disease. Steroids, in various forms, have been a pillar of therapy for both UC and Crohn’s disease. However, they should be avoided as much as possible and when used, should be taken for relatively brief period of time because of serious toxicities. The risks and benefits will be explored in further detail.
Working our way up the pyramid of medications for IBD, there is a step up to a class of medications which modulate the immune system. They act to suppress the excessive inflammation characteristic of IBD. The oldest ones, which have the longest track record of effectiveness, as well as safety, are two compounds, which get broken down by the body into the same active ingredients: Imuran (generic name is azathioprine) and Purinethol (generic name is 6-mercaptopurine). Neoral (generic name is cyclosporine) has a role for those with severe ulcerative colitis and occasionally used for a skin manifestation (pyoderma gangrenosum), which can be seen in both UC and Crohn’s disease. Methotrexate, used very widely for rheumatoid arthritis, has been shown to be effective in Crohn’s, but has no role in UC.

Remicade (generic name is infliximab), the newcomer on the block, has rapidly established itself as an important option for Crohn’s. In fact, it has revolutionized the treatment of Crohn’s for some. Remicade is the first medication approved for IBD termed a “biologic.” Biologics are targeted molecules and either have a precisely defined function or block or enhance a specific biologic pathway. They were developed along with our rapidly expanding knowledge about the immune system. Remicade is an antibody designed to bind to and block the effects of a particular molecule (TNF Alpha) which is central to the inflammation in Crohn’s. Its use is being studied in UC but is currently only approved for use in Crohn’s disease.
The first line medications, particularly helpful for UC, are the 5-ASA agents, which bring an active flare under control in UC and can also maintain remission. Often, after patients have gotten the flare under control and have been taking a 5-ASA compound for a while, they start to feel well and may question the need to take the pills each day. It is very important to know that if these agents are discontinued for six months, at least half of patients with UC will flare. The use in Crohn’s is less dramatic and sustained, but many physicians use it to get a flare of Crohn’s under control and maintain remission. Newer studies have suggested that these compounds may also reduce the risk of colon cancer.
The 5-ASA compounds can be very effective with relatively few side effects. Thousands of patients have used them for many years. Less than 5% have significant problems with 5-ASA compounds. One side effect worth noting, though rare and likely less than 1%, is that occasionally patients can develop reactions due to 5-ASA that can worsen their colitis. These compounds can be helpful in mild to moderate disease but have little role in managing severe disease.

5-ASA agents (Aminosalicylates)

**Benefits**
- Well-tolerated
- Few side effects
- Relatively inexpensive
- Oral or Rectal
- Safe for all ages & pregnancy

**Risks**
- Rare allergies/side effects
- Not helpful in severe disease
- Not helpful after steroids (particularly CD)

The 5-ASA compounds can be very effective with relatively few side effects. Thousands of patients have used them for many years. Less than 5% have significant problems with 5-ASA compounds. One side effect worth noting, though rare and likely less than 1%, is that occasionally patients can develop reactions due to 5-ASA that can worsen their colitis. These compounds can be helpful in mild to moderate disease but have little role in managing severe disease.
As many as one-third of patients taking the first discovered form of this medication, sulfasalazine, have unpleasant reactions to it, which is due, in large part, to the sulfa part of the molecule. The possible reactions can include headaches, nausea and rashes. The other part of the molecule (the non-sulfa part) turns out to be the working, or therapeutic part of the molecule, but the sulfa half is important as a chaperone to bring the rest of the compound to the colon where it is needed. If the 5-ASA compound is given alone, it gets absorbed too quickly in the small bowel and doesn’t reach the colon where it is needed. Consequently, a variety of systems were developed to deliver the 5-ASA or mesalamine compound to the colon, or where it is needed, without necessitating sulfa.

The other compounds on the list are medications, which have ingenious ways of delivering the 5-ASA portion to the intestines. Some work by gradual time-release mechanisms. Pentasa is delivered throughout the small bowel and colon, some work by the pH or acidity of the intestines. Asacol is delivered to the last part of the ileum and the colon. Dipentum and Colazal rely on the bacteria in the colon to split 5-ASA from the carrier and release it into the colon to act where it is needed. Canasa, a suppository and Rowasa, an enema are delivered directly or topically to the rectum or left colon. All seem to be similarly effective.
Another means of delivering the 5-ASA medication, other than taking it by mouth, is to put it directly on the area where the problem is: the colon. If a patient has disease limited to the left side of the colon, or just the rectum, an enema or a suppository for more limited disease can be a very effective way of bringing the disease under control and maintaining it. A medicated enema, Rowasa that delivers 5-ASA directly to the colon, can reach all the way up the left side of the colon much of the time. A Canasa suppository can deliver 5-ASA up into the rectum. In both cases, the aim is to retain the medication as long as possible by inserting the medication before bedtime and retaining it overnight. Few patients are eager to take enemas or suppositories, but they can be effective and less of an annoyance than taking pills every day.
Steroids are a two-edged sword. They have been a mainstay of therapy for Crohn’s and UC for decades. Because of their predictable toxicity for those who remain on them for extended periods, great efforts have been made to find alternative therapies to steroids and to educate physicians and patients about the serious side effects associated with their longer-term use.

In one study from Sweden, at least one-third of patients started on steroids for Crohn’s disease became dependent on them, requiring their continued use to maintain some relative improvement of their disease. A further problem is that while steroids can make some patients feel better, the goal is to heal the lining of the intestine, which steroids do not do. While there can be a role for steroids, in treating an acute flare for Crohn’s and UC, steroids are not beneficial to maintain remission. Consequently, steroids should never be used for long-term therapy, because of their toxicity and their lack of effectiveness.
When deciding whether or not to use a medication, the risks and benefits must be assessed and weighed in relation to the particular problem being treated. The issue with steroids is clear on both sides:

- Steroids can induce remission quickly and inexpensively
- They are not long term solutions

Often, particularly when a patient is taking them for the first time, steroids can provide a short-term sense of well-being. But many patients who have been on them for more than a brief period say they never want to take them again because of the side effects. In the very short term, they can be helpful, but do not provide a longer-term solution.

A partial list of the side effects are detailed above. Physicians worry most about the loss of bone density, cataracts and high blood pressure as well as other less seen medical complications. Patients are more concerned about how it makes them feel (mood swings, sleep disturbance, agitation, depression) and startling changes in their appearance (weight gain, rounded face, skin changes).
Antibiotics can be helpful for mild or moderate Crohn’s disease, as well as for perianal complications. When used for Crohn’s, they are indicated for prolonged periods of time, such as 2-3 months. Studies examining the use of antibiotics in Crohn’s are relatively few and we need better information to understand which patients can most benefit from them, but some studies have suggested that antibiotics may be more beneficial to Crohn’s colitis than to Crohn’s of the small bowel. In Crohn’s disease which is complicated by an abscess or other infection, antibiotics can play an important role as well.

Mild or moderate ulcerative colitis does not benefit from antibiotics. Some patients with severe ulcerative colitis might improve, though this is controversial.

**Antibiotics**

- Flagyl® (Metronidazole), Cipro® (Ciprofloxacin, Ampicillin, etc.)
- Treats mild symptoms of Crohn’s disease
  - Active disease when colon is involved
  - Peri-anal fistulae
- Intravenous to treat severe colitis or infections such as abscess
Antibiotics can be useful in Crohn’s disease but not in UC. Metronidazole (Flagyl) has long been used for perianal Crohn’s disease and the combination of ciprofloxacin and metronidazole has gained wider acceptance for intestinal Crohn’s disease, particularly for colonic involvement. One interesting use of antibiotics is the possible benefit immediately after surgery to decrease the risk of recurrence. As mentioned, antibiotics are used for longer periods, often several months at a time. The side effects of metronidazole are listed in this slide.

Tendon injury associated with Cipro is an uncommon injury but is worth keeping in mind as it is not the type of side effect one usually thinks of as a complication of an antibiotic.
Immune modulators can be highly effective in maintaining a long-term remission in the majority of patients. These two medications, azathioprine (with the trade name of Imuran) and its closely related metabolite or breakdown product, 6-mercaptopurine or 6-MP (with the trade name of Purinethol) are well tolerated by 90% of patients for whom they are prescribed. Some patients taking them will experience a decreased white count. Consequently blood counts are monitored throughout the time on the medication.

**Immune-Modulators**

Imuran® (azathioprine) & Purinethol® (6-MP)

- Long-term (maintenance) treatments for UC or CD
  - Can treat fistulas in CD over long-term
- Primarily for patients unable to get off steroids
- Requires continuous monitoring of blood counts
Imuran and Purinethol have been proven safe. These medications are reserved for patients who are unable to discontinue steroids or have more severe disease, which clearly requires a more potent medication and a longer-term strategy to keep the disease under control.

The most significant problem these medications present is that they take a considerable period of time to become effective, ranging from 2 months to more than 6 months before a clear effect can be seen. The side effects are usually seen in the first few weeks or up to eight weeks, which can happen at any dose. These reactions are unusual and it is unclear why they occur.

About 2-3% may get pancreatitis, less than 1% develop an inflammation in the liver, some may have a rash, fever, or nausea. Each of which will resolve when the medication is stopped. The other side effects, usually more of a problem at a higher dose, can be a decreased white count and infections, even with a normal white count.
Originally used as a treatment for childhood leukemia, immune-modulators are stigmatized as behaving like chemotherapy. Like many medications, if the risks are understood, with careful monitoring, immune-modulators can be safely and effectively used, minimizing any risk. They have been used for a variety of conditions, beginning in the 1950s and widely used in IBD particularly since 1980, so we have a great deal of information concerning their safety and efficacy. A number of myths have developed over the years not verified in the medical literature or in the data generated by numerous studies. If correctly used, most patients gain significant, long-term benefits.
A subset of individuals with ulcerative colitis has severe disease that does not respond to the usual medications. For some of these patients, hospitalized for refractory, active disease, cyclosporine can be an effective short-term bridge to other medications.

Cyclosporine was initially used as a medication to prevent the immune system from rejecting transplanted organs. Studied in patients with very active UC, who failed intravenous steroids, cyclosporine was found to be rapidly beneficial in as many as 80% of patients in this group.

While it can be effective, it also has numerous side effects that can be serious, though most are reversible. Once a patient responds to cyclosporine, in the hospital, they are switched over from the intravenous form to the oral form and are continued usually not longer than 6 months, as other medications are added. For the most part, it is useful as a bridge, buying time to allow azathioprine or 6-MP to take effect (which are medications not useful in the acute, short term setting because they take time to become active). Studies have not definitively demonstrated a similar benefit for this medication in Crohn’s disease, though it appears effective for some manifestations such as a skin condition called pyoderma gangrenosum.
Methotrexate is a medication that can be of use to treat Crohn’s disease, while studies do not support its use in UC. It is widely used in rheumatoid arthritis and has a long track record of safety. The way it works is not entirely clear, but it largely works by suppressing the immune response. Many physicians feel that methotrexate is under-utilized in Crohn’s disease.

Often used as a third line agent, after others have failed, methotrexate has been demonstrated to be useful for getting some steroid-dependent patients off steroids. In addition, many can then be maintained in remission on the medication. The side effects are relatively mild, though for some nausea can be a problem. Rarely more serious side effects can occur, such as scarring of the liver or lungs, but this is very uncommon. The medication is administered by injection, once a week, at the higher doses and can be given orally at lower doses.

This medication absolutely cannot be used in pregnancy or if a patient is trying to become pregnant as birth defects are highly likely. In addition, folic acid supplementation should be given along with this medication.
The most significant and dramatic change in therapy for Crohn’s disease in recent years has been the introduction of Remicade, known by its generic name as infliximab. Infliximab is the first of a long line of “biologics”. These medications are bioengineered medications, which are devised to act on a specific pathway or protein in the body. Dozens are now being studied and tested for the use in Inflammatory Bowel Disease.

Remicade is an antibody engineered to block a particular protein (TNF-Alpha) which is central to the inflammatory response in the body and to Crohn’s in particular. It is given as an intravenous infusion over two hours and can act within one to two weeks, even within days, to bring about stunning improvements. When given in Crohn’s initially, it is administered in three doses, the primary dose, a second dose two weeks later, the third four weeks later. Once a response is seen, a maintenance dose every 8 weeks or so, can be helpful in keeping the disease under control for many patients. It is not recommended for all patients with Crohn’s but rather for those with disease not responding to other therapies, those who are dependent on steroids and those with perianal fistulas. Remicade is currently being studied for use in UC; results of those studies will be available soon.
Given its benefits, which can be very effective for some, the downside risk is relatively low, but still significant and important to be aware of. As Remicade acts to block an important messenger of inflammation, suppressing the immune system, infection is a concern, though serious infections are not common. An infection, uncommon in the U.S. is tuberculosis. Prior to beginning the use of this medication all patients should have a skin test to determine if they have had a significant exposure to TB in the past, because Remicade can cause reactivation of latent or hibernating TB.

A primary issue of concern is that the body can react negatively to Remicade by producing its own antibody since infliximab is a foreign protein. 25% of the antibody is made up of protein derived from mouse tissue and may cause an immune reaction. A more significant problem can be the development of antibodies, which diminish the benefit of infliximab, shorten the duration or lessen the extent of response. A number of strategies can reduce the likelihood of this occurring. Lastly, infliximab is expensive (as high as a several thousand dollars per dose).
How is Remicade® administered?

- Intravenous infusion
- Allergic infusion reactions: ~20% of patients
  - Usually manageable
  - Often preventable with repeated infusions
- Discontinuation of therapy due to infusion reactions is rare

Remicade is administered as an intravenous infusion over two hours. First an intravenous line is placed. Some patients require premedication. Usually, the medication is infused without any problems and the patient does not experience anything unusual. Occasionally during an infusion, an allergic reaction can occur. Most infusion reactions can be safely dealt with by administering a mild medication prior to infusion such as Benadryl. Most infusion reactions are mild and can be well managed, without the need to discontinue the medication.
With Remicade, as with any medication, the calculation of whether it should be used for a particular patient and in a particular situation depends on the risks and benefits. In general, those medications, which are milder in their benefit, also have milder side effects. A medication with some more significant risks would not be worth trying if a patient has very mild disease that can be managed with a well-tolerated medication that has few side effects.

For Remicade, there are some potentially serious side effects, but fortunately the likelihood is low. The risk of infection, as well as a possible risk of lymphoma, is of concern. But they are not sufficiently significant to avoid its use particularly in those with significantly active disease. Some evidence suggests that Remicade can not only reduce the disease activity, but also alter the course of the disease, lessening the requirements for surgery. These benefits need to be weighed by each individual against the potential risks. Furthermore, it is not advisable to start Remicade and then stop for a prolonged period of time, such as many months, as patients can at times develop a delayed reaction which can prevent its continued use. Consequently, beginning Remicade is not a step taken lightly.
In addition to the choice of medications to treat IBD, nutrition, an area of research which is relatively neglected, is of critical importance in Crohn’s and ulcerative colitis. As these are gastrointestinal diseases, it makes sense that nutrition, or what you put into your intestine, ought to have some influence on the disease. However, the optimal diet remains to be determined.

At times, particularly when presenting in childhood or adolescence, the first symptoms of the disease can be poor growth and weight loss. While there are some guidelines and recommendations for managing the nutritional aspects of IBD, more research is needed.

Malnutrition and weight loss can be significant problems in IBD. The problem of weight loss may be due to the body's increased needs because of the inflammation. In addition, in most patients, it is not the case that the intestines are unable to absorb the necessary nutrients. The small intestine is as long as 22 feet in most patients (before surgery) and, in Crohn's, it is unusual to have such severe inflammation and so much surgery, that there is inadequate or insufficient amount of functional small intestine to interfere completely with absorption of nutrition.
Nutrition counseling for IBD is often limited to a brief bit of advice. Overzealousness in restriction of diet is not warranted. Advice from a nutritionist, particularly one familiar with Crohn’s and ulcerative colitis, can be more helpful.

While we do not have a specific diet that is ideal to help control these diseases, understanding what is a healthy diet and what foods might exacerbate symptoms can be a useful guide. A number of specific supplements and tailored diets have been developed to try to moderate the disease process itself.

Managing Nutrition in IBD

- Malnutrition can occur in IBD
  - Decreased intake of food
    - Symptoms
    - Overly zealous restriction
  - Decreased absorption of nutrients
    - Active disease, small intestine
  - Increased needs for calories and protein
- Professional nutritional assessment
- Tailor diet to individual needs & preferences
- Dietary supplements
We prefer to avoid surgery as much as possible, but sometimes it is the best therapy and often a very viable option. Needless to say, whether surgery is the appropriate therapy is a critical question. It is very helpful to have a surgeon as part of a health-care team, so that consulting only with a surgeon does not necessarily mean that surgery is the next step. Surgical options differ between ulcerative colitis and Crohn’s disease. Removing just the part of the colon that is most severe or diseased is not performed in ulcerative colitis, because the risk of recurrence in the remaining colon is so high.

In UC, the colon is removed (called a colectomy) and a new rectum or “pouch” is created out of the last part of the small bowel. The end of the bowel if turned back on itself into a “J” with the bottom of the “J” attached to the anus. A patient undergoing this operation most often has a temporary ileostomy (with an external appliance) until everything is healed, after which the ostomy is closed and the patient then evacuates in a normal way, though with some increased frequency. One function of the colon is to absorb fluid. Without it, more fluid output is generated. Typically, after having this procedure, the individual will have 4-8 pudding-like stools a day. After this surgery, though there can occasionally be other issues, the ulcerative colitis is considered cured.
In Crohn’s, surgery is not a cure, particularly when a section of the small bowel is removed and the intestines are hooked back together (an anastomosis). Recurrence of Crohn’s can be quite high, with symptomatic recurrence of 10-15% per year. As high as 80% of Crohn’s patients who have had this surgery will illustrate some evidence of recurrence of their disease, even if they are feeling generally well. The J-pouch surgery is also not a procedure usually done for Crohn’s disease, as the recurrence rate is very high and many patients will require having the pouch removed and an ileostomy created instead. However, over 80% of patients with Crohn’s who have had an ileostomy have a long-term remission and many never have recurrence of their disease.
We elect to perform a colectomy for patients with ulcerative colitis in a number of instances, for example, if the disease is acutely flaring, not responding to therapy and the individual is very ill. A variety of rare, but acute, life-threatening situations such as a perforation (a hole through the wall of the colon) or a severe bleed where a great deal of blood volume is lost, also require urgent or immediate intervention by the surgeon.

Other candidates for surgery are patients who are unresponsive to therapy, but not necessarily acutely ill. Another group of patients for whom surgery might be a useful option is those who have become dependent on steroids over an extended period of time despite attempts to wean them. Lastly, if cancer is discovered or other, more subtle "pre-cancer" warnings called dysplasia, indicate that a progression to cancer is likely, surgery is recommended.

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**Ulcerative Colitis: Indications for Surgery**

- Failure to control severe attacks or toxic megacolon
- Acute complications
- Chronic symptoms despite medical therapy
- Medication side effects without disease control
- Dysplasia or Cancer
Crohn’s can generate a number of problems we do not usually see in ulcerative colitis. A number of these complications can be indications for surgery. The chronic inflammation seen in Crohn’s can lead to local scarring which over time eventually leads to narrowing or stricturing of the intestine. These strictures can become sufficiently narrowed so that partial or complete blockages or obstructions occur, requiring surgery. No medication currently exists to reverse these strictures.

Surgery can be extremely helpful to manage perianal manifestations of Crohn’s disease, abscesses or fistulae. Toxic megacolon, a complication of severely ill Crohn’s colitis, which occurs in UC as well as Crohn’s usually, requires surgery. Another common reason for surgery is to remove a segment of intestine that has been causing persistent symptoms and is not responding to therapy.
A major concern for patients who have had long-standing colitis, whether ulcerative colitis or Crohn's colitis, is the development of colon cancer or rectal cancer. The degree of increased risk is influenced by the extent of colitis, meaning just left-sided disease or the entire colon. Patients with only the rectum involved do not have any higher risk of developing colorectal cancer than the general population.

The increased risk begins when colitis has been present for more than 8-10 years, occurring at a lower age than typical colorectal cancer in which patients over the age of 50 years begin to be at increased risk. The risk increases in proportion to the duration a patient has had colitis. Patients with a particular type of liver disease (primary sclerosing cholangitis) which occurs in a few percent of patients with UC and even less in patients with Crohn's, increases the risk even further.
A number of strategies can decrease the chance of developing colorectal cancer. Some evidence exists that taking 5-ASA compounds for an extensive period of time (sulfasalazine, mesalamine Asacol, Colazal, Dipentum, Pentasa) might contribute to lowering the risk. In addition, folic acid might lessen the likelihood of developing colorectal cancer as well.

A central approach to preventing colon cancer in IBD involves surveillance colonoscopies. For the general population without IBD, screening by a colonoscopy for colon cancer is recommended after the age of fifty. In these individuals the endoscopist is looking for polyps, little bumps of tissue, which can eventually turn into colon cancer. By removing those polyps, the risk of colon cancer can be decreased. However, the colon cancer which develops in IBD does not usually arise in polyps but in flat tissue which looks similar to surrounding tissue. There are early changes in cell architecture, called dysplasia, suggesting a progression to cancer which can be seen under the microscope. In order to find these areas, numerous biopsies must be obtained by colonoscopy, with more than 32 biopsies required for an adequate sampling. Surveillance colonoscopies are recommended after a patient has had IBD for 10 years, every 1-2 years after that until 20 years of disease, then once every year.
Another concern for the health of patients with IBD is osteoporosis. Osteoporosis is a condition or disorder affecting the bones that makes them become thinner and more likely to fracture. Osteoporosis is a problem, which can develop over years, but it would be preferable to identify the problem early. Osteopenia, which is a less severe condition, represents a milder thinning of the bones. Recently, a number of highly effective medications have been developed which not only prevent further bone loss, but actually have been shown to increase bone density as well. By identifying this problem early, the hope is to prevent fractures later in life.
A number of factors have been determined to identify those at highest risk of developing osteoporosis. Steroids such as prednisone can cause loss of bone density, which is one of the many reasons steroids are to be avoided. However, even in the absence of steroid use, patients with IBD, more with Crohn’s disease than UC, and particularly those with persistently active disease can develop this condition. The inflammation of Crohn’s disease itself can contribute to thinning of the bones.
In order to prevent osteoporosis, the aim is to detect any evidence of thinning of the bones before the problem becomes more serious. An easy quick and painless test, called a DEXA scan, is used to determine if a patient has a low bone density. A number of approaches can be helpful to prevent further loss of bone density and maintain bone health. The first goal, for many reasons, is to get the intestinal disease under good long-term control. Weight bearing exercise also helps maintain bone density. Supplemental calcium and vitamins can be helpful in maintaining bone health. A class of drugs called bisphosphonates can prevent further bone loss and also improve bone density. For patients with osteoporosis, these medications can be critical to prevent bone fractures.
Since IBD begins in many patients at an early age, a frequently encountered issue is the question of pregnancy. Is there any decrease in fertility? Are there particular problems to be aware of for the fetus? Which medications are safe? What happens to disease activity during pregnancy?

A central issue is to maintain the disease under good control, as fertility is normal if the disease is quiescent. Sulfasalazine (Azulfidine), but not the other non-sulfa 5-ASA/mesalamine compounds, can cause a decrease in sperm motility which normalizes once the sulfasalazine is discontinued. This is important for couples trying to become pregnant. If the male partner is taking sulfasalazine, becoming pregnant is likely to be difficult. In this case, sulfasalazine should be replaced by another 5-ASA compound.

If the disease is flaring when a patient is trying to become pregnant, fertility is reduced. There are no increased risks of birth defects due to Crohn’s and UC. The basic guiding principle is: “A healthy mother can give birth to a healthy baby.” For many with IBD, it is recommended they be followed throughout their pregnancy by their gastroenterologist and by an obstetrician familiar with these diseases. A “high-risk obstetrician” may be required if the disease is active or there are complications such as perirectal fistulas.
The principle guidelines, as to which medications are to be used in pregnancy, are to use those that are both safe for the fetus and essential to maintain the mother’s health. Most medications used for IBD are safe during pregnancy. During the first 6-8 weeks of pregnancy, the organs or formed. After that time, the fetus is, for the most part, just growing larger. The 5-ASA/mesalamine medications do not confer a risk to the infant; steroids are generally safe, but are associated with a small increased risk of a cleft palate. Flagyl is considered safe, even in the first trimester. Some large studies that followed a sizeable number of women pregnant on azathioprine or 6-MP support the safety of those medications in pregnancy.

**Methotrexate must be absolutely avoided in pregnancy because the likelihood of birth defects is very high.**
Research in IBD

Where are We Heading?

Research drives forward advances in these diseases. While some of the research involves test tubes and mice, a critical component is studies which involve patients who have these diseases. Some studies aim to determine if a particular medication is beneficial. Others involve drawing blood to search for a gene that might lead to IBD. Another type of study may involve questionnaires, having patients with IBD fill in a long list of questions.

Research studies require a number of components. First is a researcher or a group of researchers interested and motivated to study the question or project. Then the project must have adequate resources to complete the task such as a facility or institution that is supportive. And sufficient funds must be available to conduct and complete the study. In order to conduct any study involving a patient, whether administering a drug, drawing blood, performing a colonoscopy, taking a biopsy or even answering a questionnaire, requires the review and approval of an Institutional Review Board in place to protect the rights, interests and safety of those being studied.

But greater than anything else, the research requires the critical participation of patients with UC and Crohn’s, and often their relatives and friends as well. By participating in these studies, patients with Crohn’s or UC have an opportunity not only to help themselves, but also to assist in the crucial and important endeavor to expand the knowledge about these diseases and provide an important service for the broader community of IBD.
One gene defect (NOD2), as discussed earlier, has been associated with 20-30% of patients in the U.S. with Crohn’s disease. This is the beginning of the search for a number of other genetic abnormalities linked to Crohn’s and ulcerative colitis. These studies are time intensive. The hunt for IBD-related genes requires collecting blood samples and information from patients with IBD and their relatives, to determine which areas of chromosomes tend to be inherited by those with IBD compared to the brother, sister or parent who does not have the disease, narrowing down on a site within a region on the chromosome, and then finding out which of the 30-40,000 genes humans possess, has the defect.

In Crohn’s and UC, it may be that not one gene but several genes must be inherited together to predispose the development of the disease. The identification of a gene is just the beginning of a long process of how the gene operates in a healthy patient and how it malfunctions in IBD. Ultimately, manipulating genes may be a therapy for IBD. The first such trials are currently being planned in Europe. The identification of the gene provides crucial insight into the disease process so that, in understanding the genesis of these diseases, we can develop safe and effective approaches to treating or preventing IBD.
IBD results from an interplay of environment and genetics. A central part of the environment is the bacteria to which the intestines are exposed. Understanding that environment better and identifying which components may be related to the development of Crohn’s or UC will provide important parts of the puzzle. There are a number of bacteria or viruses that some researchers have attempted to link to IBD. Most researchers feel the data does not support such claims. Others have proposed that Crohn’s disease may result from a chronic infection with the measles virus while others have advanced tuberculosis-like bacteria called “Mycobacteria Paratuberculosis” as being the culprit. It is important to keep in mind that, by some accounts, over 80 different infectious organisms have been proposed over the years as the cause of Crohn’s or ulcerative colitis but none have generated data proving the case or has thus far withstood the challenges of further investigations.

Another critical puzzle part in understanding IBD, is the immune system and deciphering how it is abnormal in IBD. The nature of the interaction between the so-called normal bacteria and the immune system is the focus of considerable effort. As our knowledge of the immune system expands, it is applied to IBD, to gain insight into the complex interactions, which are at the heart of IBD. Whether IBD results from an abnormal reaction to “normal” bacteria, or the immune system mistakes part of the intestines or colon as a potential bacterial or viral threat (autoimmune theory particularly with regard to UC), each of these ideas must be investigated as possible keys to unlocking the puzzle of IBD.
If specific environmental causes are identified, a variety of therapeutic approaches could be utilized to treat that cause. If a particular organism is identified, then tests would be developed to determine which individuals have disease associated with the organism. Most researchers feel it is unlikely to be a typical or straightforward infection, as is conventionally understood. We know that IBD does not appear to be a typical infectious disease, since exposure of people without IBD to patients with IBD does not produce the disease. However, an abnormal immune response to an organism could be at the core of IBD and eradicating the organism from a patient could alleviate the underlying problem. Lastly, the hope would be to have a long-term solution through a vaccine to immunize people against a particular causative organism. At present such an organism has not been convincingly identified and no program of immunization is being planned. With further research, such a hope might be realized.
Research is being conducted for an enormous variety of issues: the pathophysiology (or causative pathways which lead to IBD), genetics, identifying the environmental risk factors, understanding why IBD progresses more severely in some than in others, why some suffer from certain complications, what medications are beneficial, etc. Surgery or related issues are being intensively researched as well.

Some patients (5-15%) who have a “J pouch” or ileo-anal pouches can develop chronic inflammation in the pouch known as “pouchitis.” Many will have one acute episode quickly responding to antibiotics, whereas, the pouchitis may become chronic in 10% of these patients. New approaches to understand pouchitis, why it develops and how it can be best treated or prevented, are being researched.

New surgical techniques are being explored. One current surgical trial is investigating which type of anastamosis (connection of the intestines after a resection) will reduce the recurrence rate of Crohn’s disease. In addition, medications that will prevent or delay recurrence of disease (after a surgical resection has eliminated the active disease) is an area of important research.
IBD, ulcerative colitis and Crohn’s disease, are life-long diseases. Broad advances in nearly every aspect of IBD have expanded our understanding of these diseases: who is at risk for developing them, what environmental influences affect Crohn’s and UC, the genetics of these diseases, the nature of the immune dysfunction which is at the heart of the disease, what proteins are increased that drive the inflammatory response, what medications can be used and how they should be used to safely control the inflammation. People throughout the world are engaged in an intensive, sustained effort to push these advances further to improve our understanding and treatment of these diseases. The research continues.

As a patient with IBD or a friend, relative or loved one of a patient with IBD, it is important for your physical and emotional health to be part of these endeavors:

• Participate in the research
• Keep up with the advances
• Learn about the progress being made

This slide presentation is just the beginning of a sustained involvement in this process.
This one is difficult to understand. I can’t quite figure it out, the next one is better.
This one is a lot easier to understand. If the patient takes their medication, even after 2 years, it looks like maybe 90% or higher were still in remission. Of the patients NOT taking their medication as they are supposed to, it drops down to maybe 35% or 40%. And the trend is downward, so it would get even worse over time, where as if you stay on your medication, remission stays high.
for more information:
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