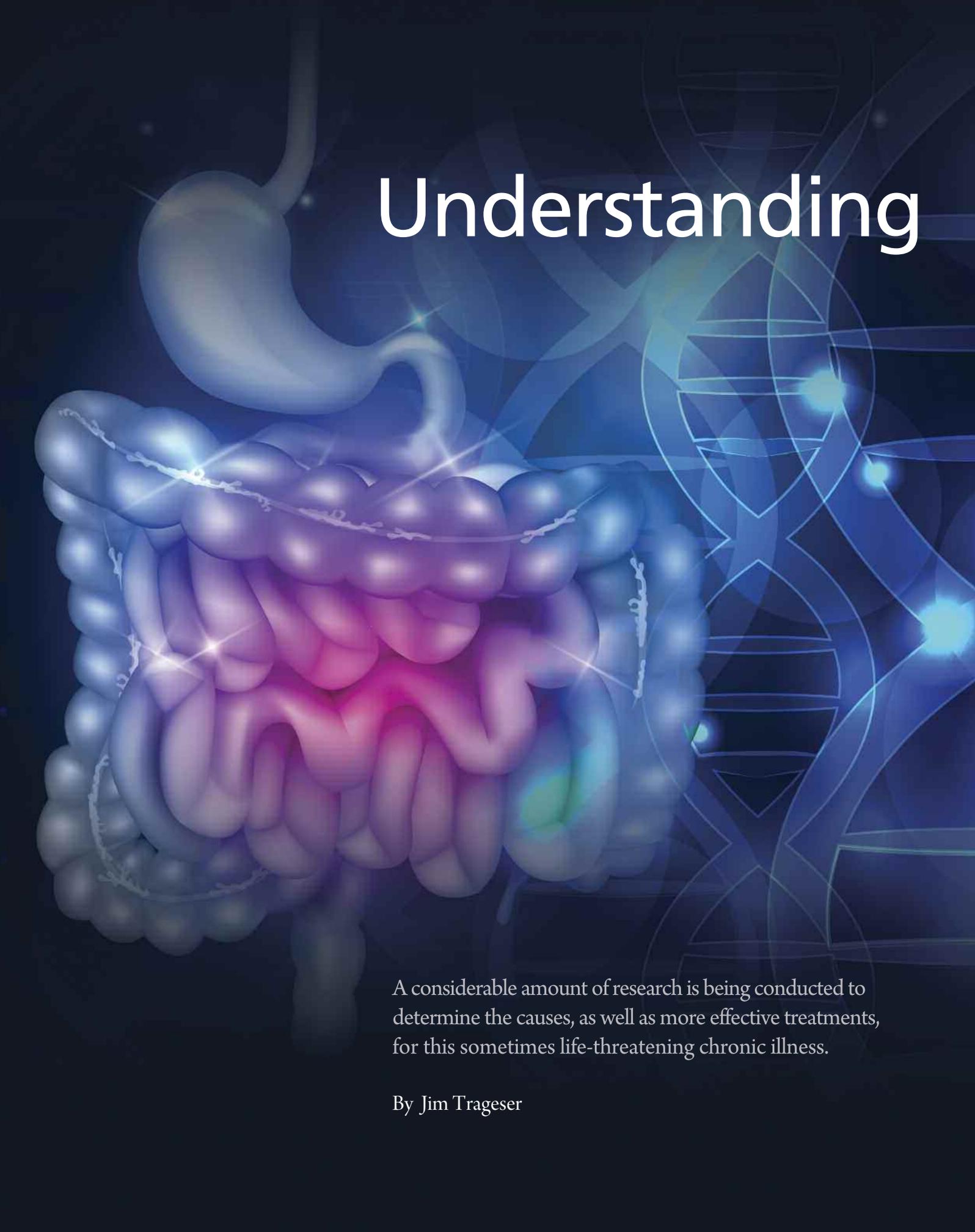


Understanding



A considerable amount of research is being conducted to determine the causes, as well as more effective treatments, for this sometimes life-threatening chronic illness.

By Jim Trageser

Crohn's Disease

WITHOUT A CLEAR understanding of its underlying causes, a cure or even a single test to make a diagnosis, Crohn's disease remains a baffling chronic illness that presents many primary immunodeficiency patients and their physicians with an ongoing set of challenges for addressing its significant health risks. This inflammatory bowel disease (IBD) initially manifests as gastrointestinal (GI) distress, but it can progress to life-threatening blockages and ulcers, requiring emergency surgical intervention. Even in the majority of cases, when patients enjoy long periods of remission, Crohn's requires constant monitoring and persistent dietary and lifestyle changes that demand close cooperation between patients and their physicians.

What Is Crohn's Disease?

Crohn's was first described as a specific subset of IBD in a 1932 article written by Burrill Bernard Crohn, MD, of New York City's Mount Sinai Hospital. A follow-up paper was cowritten with fellow physicians Leon Ginzburg and Gordon Oppenheimer, but Crohn's name was listed first due to alphabetical precedent, and the condition became known as Crohn's disease.

Crohn's is a chronic IBD that affects the lining of the digestive tract.¹ Any part of the GI system can be affected, from the mouth to the anus,² although the most common areas affected are the lower large intestine near the anus (the sigmoid colon), and the area of the small intestine nearest the large intestine (the ileum).³ Crohn's is differentiated from other IBDs by the specific type of lesions found in the digestive tract, as well as the types of ulcers and fistulas that develop in severe cases.

Mild cases affect only the innermost layer of the GI tract, the mucosa, which becomes inflamed. However, the disease can also affect deeper layers, and in severe cases becomes life-threatening due to the development of blockages, ulcers or fistulas³ that can require surgery to repair. Healthy segments of the intestines can exist alongside diseased segments, with abrupt transitions between affected and healthy tissue.⁴ Children with the disease often exhibit stunted growth and delayed puberty due to the lack of nutrients processed by the diseased GI tract.⁵

Crohn's is categorized into five subtypes, based on the location of the inflammation:⁶

- **Ileocolitis:** This is the most common type, which affects the ileum, occurring in approximately 45 percent of Crohn's patients.
- **Ileitis:** This type, occurring in approximately 30 percent of Crohn's patients, also affects the ileum, but it is more severe and can lead to the formation of abscesses or fistulas, or abnormal tubes between the intestines and the abdomen or skin.
- **Granulomatous:** One-fifth of all Crohn's patients have this type, affecting the main part of the large intestine, including the sigmoid.
- **Gastroduodenal:** This relatively rare type affects the area between the stomach and the small intestine, affecting only about 5 percent of patients.
- **Jejunioileitis:** The remaining 5 percent of patients develop this type, which affects the main part of the small intestine.

Crohn's generally manifests in the late teens or 20s, although it can appear at any age.⁷ People of European ancestry are at slightly higher risk, particularly Ashkenazi Jews.² It is also more prevalent in developed nations and urban areas.⁸

CROHN'S IS CATEGORIZED INTO FIVE SUBTYPES, BASED ON THE LOCATION OF THE INFLAMMATION.

Roughly 780,000 Americans have Crohn's at any time,⁹ according to the Crohn's and Colitis Foundation of America. However, a Crohn's disease information website hosted by AbbVie Inc., a U.S. pharmaceutical firm, puts the number at 700,000,¹⁰ while a 2016 *USA Today* report cites 570,000.¹¹ The Centers for Disease Control and Prevention cautions that due to inconsistent definitions and diagnoses, a precise number cannot be known.¹²

Of those with the disease, nearly half are in remission, 30 percent have a mild case, 20 percent have a moderately severe case and 2 percent have a severe case.⁹ This will change in each patient, however, and roughly 75 percent of patients with Crohn's will require surgery at some point in their lives.

Causes of Crohn's Disease

The cause of Crohn's is not presently understood. Researchers are looking at a variety of possible causes, ranging from immune system disorders to genetics. It is not currently believed that stress or diet play a role in triggering Crohn's,¹³ although smoking tobacco is associated with both increased risk and severity of disease.⁸

While most people with Crohn's do not have a family history of it, it is still more prevalent in some families than others, meaning there may be a hereditary predisposition.⁸

DIARRHEA, CRAMPING, BLOATING, GAS, FEVER AND FATIGUE ARE ALL COMMON SYMPTOMS OF CROHN'S IN ITS EARLY STAGES.

Numerous studies are ongoing to try to determine the cause — or, more likely, causes — of Crohn's. One recent study suggests it may be the result of a specific combination of bacteria and fungi in the digestive tract.¹¹ Another recent study, built upon earlier studies that looked into genetic links to Crohn's, found a series of mutations of genes that regulate the body's ability to react to the presence of bacteria in the digestive tract. It is thought that the inability to recognize these bacteria as normal and necessary may cause the body to react in a way that damages the body itself.¹⁴

Symptoms and Progression of Crohn's Disease

The first symptoms of Crohn's are similar to those of other IBDs and numerous other unrelated GI afflictions.

Diarrhea, cramping, bloating, gas, fever and fatigue are all common symptoms of Crohn's in its early stages. Those with a more severe case may also exhibit oral ulcers, bloody stool and anal drainage.¹⁵ Depending on the location of the inflammation, patients may experience unexplained and unplanned weight loss due to intestines' inability to extract nutrients from food.

As the disease progresses, it can lead to GI strictures (which can produce obstructive symptoms such as vomiting, bloating, severe abdominal distress and distension), ulcers or fistulas. In

rare cases, the disease's severity will spread to the skin, blood and even endocrine system (known as extra-intestinal manifestations, or EIMs).¹⁶ Pyoderma gangrenosum, which is associated with Crohn's (and ulcerative colitis), is a deep skin ulcer often found on the legs. Other EIMs include episcleritis (inflammation of the eye), some types of arthritis and erythema nodosum (red nodules on the skin, usually near the ankles).¹⁶

If the disease affects the small intestine in those diagnosed before adulthood, the resulting malnutrition will lead to growth retardation or delayed onset of puberty.¹⁷

In most patients, Crohn's is marked by long periods of remission, punctuated by periodic flare-ups of varying severity.

Diagnosing Crohn's Disease

Because of the similarity of Crohn's symptoms to other GI maladies, and because Crohn's is a definition based on symptoms, making a specific diagnosis can be challenging. For instance, differentiating between Crohn's affecting the large intestine and ulcerative colitis can sometimes prove impossible, leading to a diagnosis of indeterminate colitis.¹⁸

A diagnosis of Crohn's will most often result from eliminating other possible causes for symptoms experienced by patients. While GI symptoms are similar to those of many other diseases, ranging from indigestion to cancer, the presence of any EIMs alongside diarrhea, cramping, etc., can strongly indicate the possibility of Crohn's or other IBD.

As other explanations are ruled out and Crohn's becomes a possible diagnosis, there are a variety of tools available. An endoscopy can be ordered to visually look at the internal damage to the GI tract and take biopsies. Depending on the specific symptoms and results of prior tests, the physician may order a colonoscopy to check the large intestine, an upper GI endoscopy to inspect the stomach and duodenum, or an enteroscopy to look at the small intestine. Biopsies will be examined for the presence of granulomas, which can indicate Crohn's. If a physician isn't sure which part of the digestive tract is symptomatic, or if there is a need for a fuller picture of the patient's GI system, then a capsule endoscopy may be used.¹⁹ A computed tomography scan or magnetic resonance image may also be ordered to look for damage consistent with Crohn's.²⁰

Treating Crohn's Disease

There is presently no way to prevent Crohn's, and there is no cure. Treatments vary widely depending on where in the patient's GI tract it manifests, how severe the case is and the patient's age and overall health.

While surgery is often necessary to remove strictures or other heavily damaged segments of the intestinal tract, or to repair or remove ulcers, most physicians will begin with a medication regimen and diet and lifestyle changes. The goal of Crohn's treatment is to induce remission and sustain it as long as possible to reduce the number and severity of flare-ups.²¹

Treatment generally begins with an anti-inflammatory drug to try to control symptoms and, hopefully, promote remission. Anti-inflammatory drugs used to treat Crohn's fall into two broad categories: aminosalicylates (which have been used to treat Crohn's disease for more than 30 years) and corticosteroids. Both classes of drugs cause significant side effects, and neither is 100 percent effective at bringing about improvement in all patients. The patient's history, specifics of the disease and overall health will help the physician devise the best approach.

Aminosalicylates, according to the National Institutes of Health's National Institute of Diabetes and Digestive and Kidney Diseases, are used by many physicians to treat new, mild cases of Crohn's. This class of drugs, which is administered orally, includes balsalazide, mesalamine, olsalazine and sulfasalazine.²² Unfortunately, the side effects are often the same as the symptoms from Crohn's: diarrhea, vomiting, nausea and abdominal pain. However, some studies indicate that mesalamine can induce remission in about half of patients who receive it.²³

According to Britain's National Health Service, corticosteroids are also used first by many doctors.²¹ Prednisolone can be taken orally, or hydrocortisone can be given via injection. However, due to the numerous side effects (facial swelling, weight gain, reduced immune response, weakening of the bones), corticosteroids are generally only prescribed for short durations. And, some patients will not respond to corticosteroids.

If anti-inflammatory drugs are not successful, then other, more powerful — and potentially dangerous — drugs may be tried. These include immunosuppressant drugs, TNF inhibitors, ustekinumab, cyclosporine and high-dose immune globulin (IG).

The most widely used immunosuppressant drugs include azathioprine (Imuran) and mercaptopurine (Purinethol).²⁴ Potential side effects include higher risk of infection and some cancers, as well as inflammation of the liver and pancreas, so they require regular monitoring.

Tumor necrosis factor (TNF) inhibitors are used for moderate to severe cases of Crohn's. These powerful drugs work by neutralizing the TNF protein in the body's immune system, and include infliximab (Remicade), adalimumab (Humira) and

certolizumab pegol (Cimzia). These drugs cannot be used in any patient with tuberculosis or other serious infections. They have proven effective in helping patients who have developed fistulas as a result of Crohn's, and they may also help induce remission.²⁴ Use of these drugs is also tied to an increased risk of certain cancers.

Ustekinumab (Stelara), which inhibits production of interleukin 12 and interleukin 23, has also shown some promise in controlling symptoms of Crohn's, specifically in patients who show no or only temporary improvement as a result of TNF inhibitors.²⁵ (Interleukins are a class of cytokines secreted by white blood cells as part of the body's regulation of its immune system.)

Cyclosporine (Gengraf, Neoral, Sandimmune) and tacrolimus (Astagraf XL, Hecoria) can also be used to treat those with fistulas when other drugs have proved ineffective. Again, the potential side effects are serious: kidney and liver damage, seizures and even potentially lethal infections.²⁴

High-dose IG has shown promise in inducing remission. While the data pool is currently small, a 2014 study showed that both intravenous and subcutaneous IG had been used with patients who subsequently entered remission. However, the study's authors argued that these results warrant further study.²⁶

TREATMENT GENERALLY BEGINS WITH AN ANTI-INFLAMMATORY DRUG TO TRY TO CONTROL SYMPTOMS AND, HOPEFULLY, PROMOTE REMISSION.

In many cases, other medications — most often, antibiotics and over-the-counter painkillers — are used in combination with one of the above drugs to ameliorate side effects.²⁷

There are also other treatment approaches. One is to introduce parasites into the GI tract. A 2015 study that showed the presence of hookworms was associated with a higher incidence of remission suggests the ability of parasites to regulate the body's immune system to promote their own survival.²⁸ Another is bowel rest in which patients are put on a liquid diet, intravenous

solution or feeding tube to give the GI tract a few days or longer off to allow inflammation to subside.²²

When none of these strategies proves effective, surgery can become unavoidable, with some 75 percent of patients requiring it at some point.²⁹ The introduction of laparoscopic surgical techniques has reduced the risks, as well as recovery times and the length of hospitalization, but it is not an option for all procedures. Common surgical interventions will deal with strictures, abscesses or ulcers. In some cases, sections of the intestines or colon are removed if they are too damaged. The most serious cases of Crohn's can lead to ileostomy, in which the colon and anus are removed, which has serious quality-of-life implications for patients.²⁹

THERE ARE CURRENTLY MORE THAN 1,000 ONGOING CLINICAL STUDIES FOR CROHN'S DISEASE.

Treating most EIMs involves effectively addressing the underlying Crohn's that is causing them. For example, because of the seriousness of pyoderma gangrenosum, it may need to be treated apart from Crohn's. Immunosuppression is the most commonly used treatment for pyoderma gangrenosum, although corticosteroids are also sometimes used.³⁰

Due to the heightened risk of developing cancer with Crohn's, most physicians will schedule more frequent endoscopic examinations as part of patients' ongoing treatment.

In addition to all of the above, another important part of treatment is working with patients to help them control the severity of symptoms and reduce the likelihood of flare-ups. Patients can do this by watching their diet and, if they smoke, by stopping. Studies indicate that limiting the amount of dairy and fried foods, eating smaller portions more frequently and keeping on eye on fiber can all help moderate symptoms.³¹ Juvenile patients whose Crohn's is affecting their growth rate or sexual development can reverse those particular effects with nutritional support.¹⁷

Finally, having a serious chronic condition like Crohn's is a frightening and emotionally draining experience for patients. Therefore, they should be encouraged to join a support group

to help them deal with the emotional turmoil. The Crohn's and Colitis Foundation of America maintains a database of local support groups.³² For patients exhibiting higher than expected stress in dealing with their condition, a referral to a therapist may be useful.³³

Ongoing Research

There are currently more than 1,000 ongoing clinical studies for Crohn's disease. The British National Health Service lists 1,356 clinical studies just in the United Kingdom and U.S. as of this writing.³⁴ The U.S. federal government's ClinicalTrials.gov lists 307 (with duplicates between the two lists).

Research into Crohn's is proceeding on multiple fronts: learning what causes it, finding more effective treatments and searching for a cure. Discovering what causes Crohn's is most critical because it will obviously allow for more effective and efficient treatments, as well as a clearer path toward an eventual cure.

The Crohn's and Colitis Foundation of America underwrites the Broad Medical Research Program, which has invested \$50 million over the past 15 years into basic research regarding Crohn's. The foundation aims to raise \$2 million per year to put back into primary research. In addition, it is underwriting two other interrelated research programs titled the Genetics Initiative and the Microbiome Initiative. These two programs fund and encourage studies to identify those genes specifically tied to a likelihood of developing Crohn's, as well as identifying specific bacteria and fungi in the digestive tract. Other initiatives are funding research into pediatric IBD and IBD and pregnancy.

Among the more than 1,300 studies underway in the U.S. and United Kingdom are those to determine the long-term effects and efficacy of dozens of existing medications. Other studies are looking at genetic markers, vitamin supplements to assist juveniles with Crohn's, using patients' own fat to grow stem cells to repair fistulas, new surgical techniques to reduce the impact on patients' quality of life, and new electronic imaging processes to minimize invasive diagnostic testing.

And, there are new medications well into the study pipeline showing real promise:

- Mongersen is an antisense oligonucleotide that targets SMAD7, a protein involved in the body's regulatory system. Early results of an ongoing study at the University of California, San Diego, found that some 60 percent of patients who received Mongersen entered remission.³⁵

- A Finnish study looking at the molecular level of the immune regulatory system suggests that use of the anti-rejection medication daclizumab (Zinbryta) may be useful in treating Crohn's, as well as multiple sclerosis.³⁶

There are also some other interesting studies:

- Looking into the interplay between human genes and the naturally occurring microbes that assist with digestion in the GI tract, a 2016 study involving U.S., French and Belgian researchers looked at the population composition of the microbiome (the community of microorganisms naturally occurring in the human digestive tract) of patients with Crohn's and their family members without Crohn's. They found a marked difference in the makeup of microbes in those who had Crohn's versus those who did not. It is not yet known whether this is a result of the changed environment of a GI tract with Crohn's, or a contributing cause, but it does offer insight into possible treatment options.³⁷

- An article in *Nature Immunology* argues that introducing certain beneficial bacteria into the GI tract can help reduce inflammation. Examinations of the microbiome showed that in patients with Crohn's, the ratio of different species was different than in healthy patients, and by artificially restoring the healthy ratio, inflammation was reduced.³⁸

- A study at Arizona State University has identified unique biomarkers that only appear in blood samples of those with Crohn's, suggesting a one-step blood test for diagnosing is possible.³⁹

- An analysis of previous studies suggests that while anti-inflammatory drugs can be effective at relieving symptoms, they do not promote healing of the mucosa layer of the GI tract. On the other hand, several TNF inhibitors — infliximab and adalimumab — have shown promise in promoting healing of the tissue scarred by Crohn's.⁴⁰

Looking Ahead

As physicians work with their patients to help them maintain as high a quality of life as possible, and to avoid the kinds of life-altering surgical procedures that Crohn's can require, it is likely that new techniques, drugs and treatments will continue to arrive yearly, if not more often.

Inoculation and/or a cure may be beyond the current horizon, but treatment options that maximize patient quality of life are in the pipeline and on the way. ❖

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