

# Inflammatory Bowel Disease

**Inflammatory Bowel Disease affects the intestine and causes great pain and discomfort. Whilst modern treatments help make life tolerable, there is a lot of research into advances that will help millions lead a more normal life.**

## What is inflammatory bowel disease?

There are two major forms of inflammatory bowel disease (IBD): ulcerative colitis and Crohn's disease. Key differences between them are shown in the table, although it may not always be possible to distinguish them with certainty. The main feature of IBD is inflammation of the lining of the intestine, leading to ulceration, pain, diarrhoea (which is bloody in ulcerative colitis) and bowel obstruction (in Crohn's disease). Both diseases typically have an unpredictable relapsing/remitting chronic course, with the risk of anaemia, malnutrition, difficulty in maintaining body salt balance and an enhanced risk of developing bowel cancer.

**Table: Key differences between ulcerative colitis and Crohn's disease**

	ULCERATIVE COLITIS	CROHN'S DISEASE
Parts affected	Large intestine and rectum only	Any part of the digestive tract from the mouth to the rectum
Areas inflamed	Only the lining of the intestine is inflamed	All layers of the digestive tract may be inflamed

It is now generally believed that IBD is caused when three main factors interact inappropriately, possibly in association with dietary elements: our individual genes, our immune system and the bacteria living in the gut. The genes suspected so far are scattered on different chromosomes, notably 3, 5, 6, 7, 12 and 16.

The 400 square metres of the intestinal absorptive area is the largest single surface in or on the human body. The single layer of cells lining the intestinal digestive tract is constantly exposed to high levels of bacteria and pathogens. A mutation in a gene known as NOD2 on chromosome 16 has been found to increase markedly susceptibility to Crohn's disease, but not to ulcerative colitis. A protein product of this gene is involved in the recognition by cells in the gut of a bacterial membrane component called lipopolysaccharide, and an inappropriate immune response to gut bacteria, with migration of inflammatory leukocytes into the epithelium, has been suggested as a causative mechanism in Crohn's disease.

Researchers also believe the protein encoded by the Crohn's disease susceptibility gene NLRP3, cryopyrin, is an intracellular bacteria sensor that plays a key role in initiating immune response. This bacterial sensor is probably defective in some patients, and doesn't correctly recognise the presence of harmful bacteria.



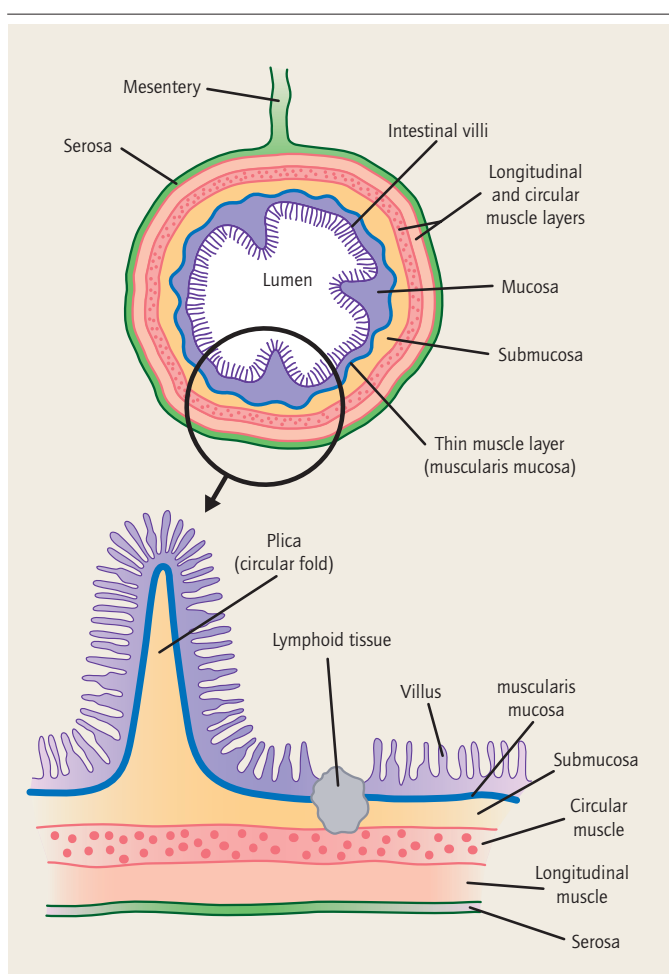
### Who gets ulcerative colitis and Crohn's disease?

Ulcerative colitis affects some 500,000 people in the EU and 30,000 new cases are diagnosed each year. About 250,000 people suffer from Crohn's disease, with around 18,000 new cases per year. Because of under-recording, European health experts presume that the true number of people suffering from IBD in the EU may be nearer a million. Crohn's disease is found throughout the world. However, it appears to be most common in North America and northern Europe, and Canada has one of the highest incidence rates in the world. The age of onset of both diseases peaks between the ages of 15 and 30-35 and men and women are equally affected.

### Present treatments:

Management of the acute phase of IBD commonly involves symptomatic relief with antidiarrhoeal medicines, nutritional support and the use of anti-inflammatory steroids, which induce complete or partial remission in about 80 per cent of cases. In severe cases, immunosuppressive medication may be necessary.

Once the acute symptoms have been controlled, remission is usually maintained through the use of 5-amino-salicylate derivatives. All are approved for use in ulcerative colitis, but only one compound is indicated for Crohn's disease as well. Salicylates work by the inhibition of 5-lipoxygenase and various hormones which induce inflammation (cytokines), and may also be used for acute treatment in mild to moderate ulcerative colitis. They tend to be less effective than steroids. Where the disease is confined to the rectum and lower part of the colon, medication may be administered in the form of suppositories or enemas.



Diagrammatic cross section of the human small intestine

IBD is a disorder in which inflammatory cytokines such as tumour necrosis factor *alpha* (TNF-*alpha*), interferon *gamma* and interleukin-1 are overproduced. These can result in local tissue damage. If they could be controlled, the disease itself might be controlled or eliminated. Several research groups have recognised the potential this provides and the most popular target in recent years for intervention has been TNF-*alpha*. Anti-TNF-*alpha* products are available in Europe for the maintenance treatment of severe active and fistulising Crohn's disease.

Further anti-TNF *alpha* products are being tested to show that the compounds may allow withdrawal of steroids in disease remission. Also available is a pegylated monoclonal antibody directed against the same antigen which is administered through a once-monthly subcutaneous injection, rather than an intravenous infusion.

In severe IBD that does not respond to medicines, surgical removal of the diseased segment of the intestine may be necessary. About 75 per cent of people with Crohn's eventually need surgery, compared to only about 20 per cent in ulcerative colitis. Surgical removal of large sections of the intestine can result in short bowel syndrome – a serious and potentially life-threatening condition. A recombinant somatotropin product is for use in this indication.

### What's in the development pipeline?

Approaches include further anti-TNF *alpha* molecules, investigations with a recombinant TNF binding protein in Crohn's disease, and the development of an inhibitor of the enzyme that produces TNF *alpha*. Interferon *beta-1a* is in Phase 3 trials in ulcerative colitis. Haematopoietic growth factor for white blood cells is being investigated in Phase 3 trials in Crohn's.

*Alpha*<sub>4</sub>-integrins are important in the adhesion of leukocytes to blood vessel walls and their subsequent migration into underlying tissue, such as the tissue of the gut, where they can contribute to the inflammatory response seen in IBD. Investigations are being carried out on a humanised monoclonal antibody that inhibits *alpha*<sub>4</sub>-integrin. Clinical results obtained in people with Crohn's showed a marked decrease in disease activity, but results of further clinical trials must be awaited.

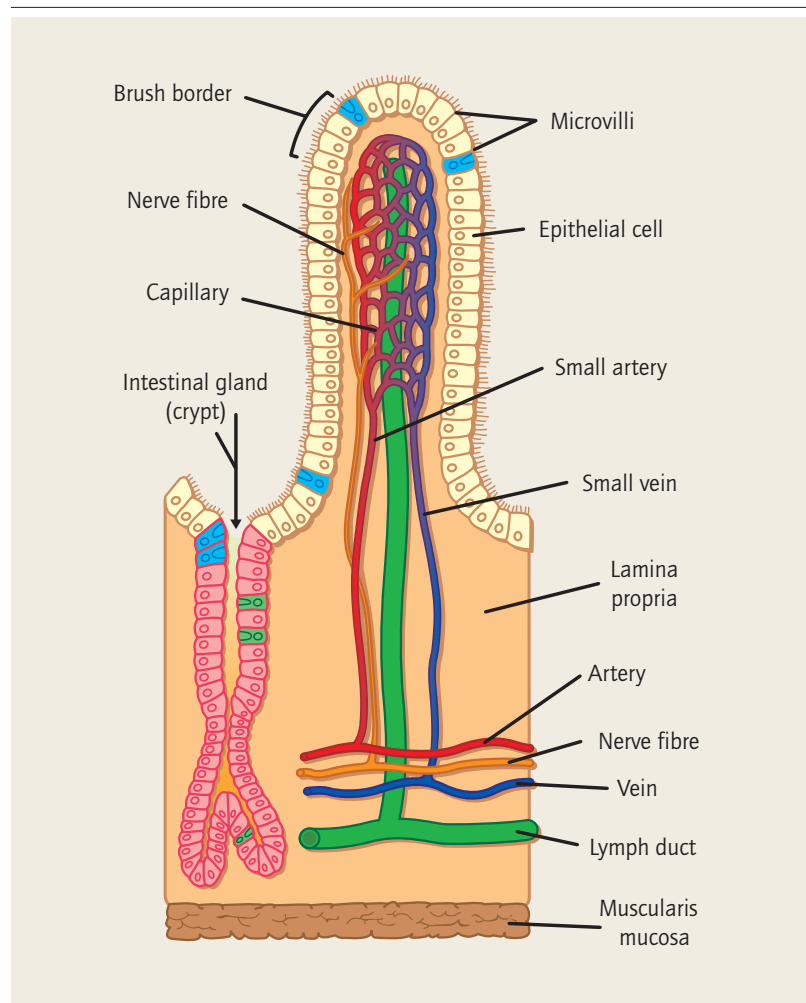
Steroid derivatives also continue to be developed for IBD. Here, research focuses on an oral steroid which is active locally in the gut but produces only low levels in the blood, which should reduce the incidence of side-effects. Another research group uses a colonic drug delivery system (enema formulation) to release a corticosteroid locally in the intestine, with the same objective of reducing systemic side-effects.

Epidermal growth factor (EGF) enemas may provide another new avenue for ulcerative colitis. An enema rather than oral formulation is necessary, as the protein would be broken down in the upper gastrointestinal tract. Research suggests that EGF might exert its beneficial effect by facilitating the repair of damaged intestinal cells, and thereby stopping antigens from irritating the lining of the colon.

A number of other pathways and mechanisms probably play a part in IBD. One is the CD40 pathway that is involved in both antibody responses and in the processes of cell-to-cell contact that occurs in the inflamed bowel. New antibodies are being investigated that block this pathway. Assessment is also carried out on small molecules that mimic an enzyme found in inflammation that is involved in trapping reactive forms of oxygen.

### The longer-term future:

Several more approaches to IBD are in development. One is treatment with anti-*gamma* interferon antibody in Crohn's disease. The cell adhesion molecule ICAM-1, a glycoprotein cell recognition molecule involved in inflammatory response is the target of an antisense inhibitor that has already shown clinical benefit in active ulcerative colitis in a Phase 2 trial. Meanwhile, an enema formulation of the antisense product is available.



Detailed structure of a villus showing the rich provision of blood vessels, nerves, and lymph ducts in the underlying lamina propria

PPAR *gamma*, a receptor of great interest in diabetes research, can inhibit tissue injury associated with immune activation, and hence may be a future target in IBD, as may the transcription factor Nuclear Factor- $\kappa$ B. In view of the large number of molecules involved in the disease process in both ulcerative colitis and Crohn's disease, there is no shortage of future medicine development targets and substantial research efforts can be expected to continue. Many of the symptoms of IBD are disabling in their own right, so medicines that can help control these help make life more tolerable for people with the disease.



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Design & Production - Megaluna

Last update: July 2009