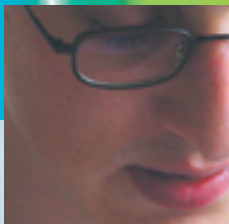


Crohn's disease and its associated disorders



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FALK FOUNDATION e.V.



Leinenweberstr. 5
79108 Freiburg
Germany

www.falkfoundation.org

For further information please contact

DR. FALK PHARMA UK LTD



Bourne End Business Park
Cores End Road
Bourne End
Bucks SL8 5AS
United Kingdom

www.drFalk.co.uk

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Crohn's disease and its associated disorders

Author

Prof. Dr. Volker Gross

Klinikum St. Marien

Medizinische Klinik II

Mariahilfbergweg 7

92224 Amberg

Germany

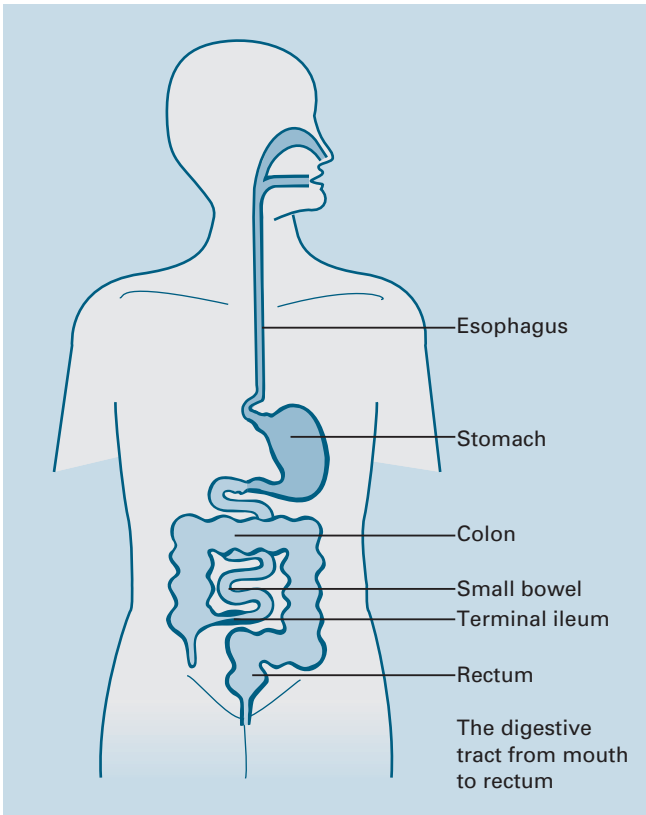
E-Mail: gross.volker@klinikum-amberg.de

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Crohn's disease: What does this diagnosis mean?

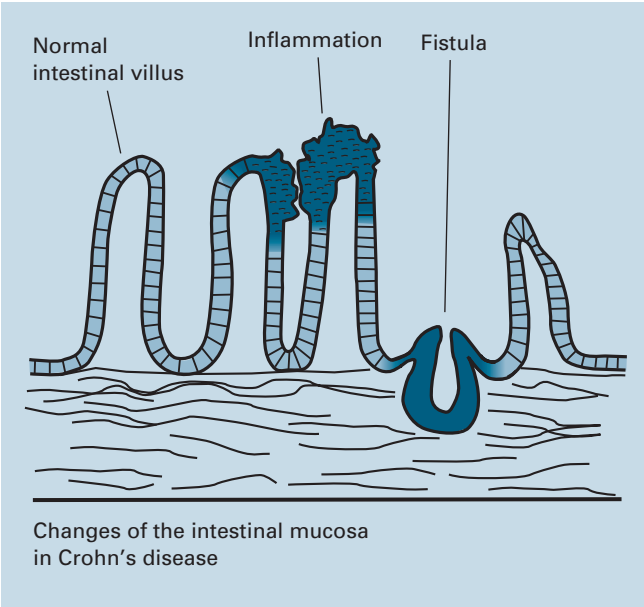
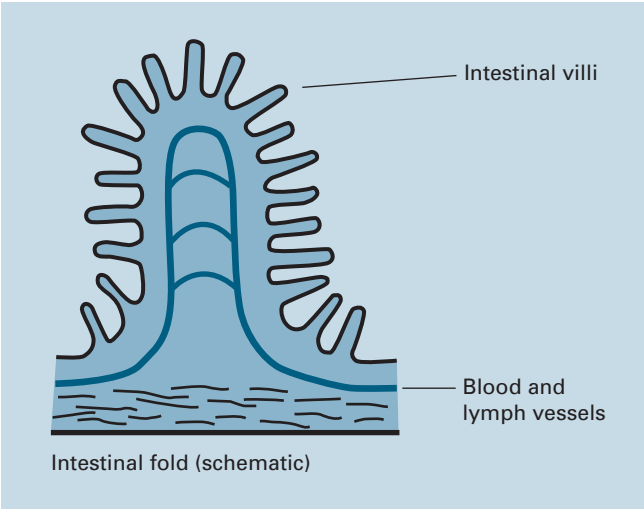
The disorder now known as Crohn's disease was first described in 1932 by the American gastroenterologist, Burrill B. Crohn. Working in New York, Crohn recognized it as an inflammatory disease of the small bowel that follows a chronic course and results in scarring of the bowel. Because it most often involves the last, or terminal, segment of the small bowel (also called the ileum), the disease is also known as *terminal ileitis*.



Crohn's disease can affect people of any age and may occur even in children. In most cases, however, the disease strikes young adults aged 20–40 years. Children with Crohn's disease require particularly careful and comprehensive treatment that starts as early as possible. If the disorder is not recognized, the untreated intestinal inflammation can lead to growth disturbances, delayed puberty and even reduced scholastic capability. Although the disease predominantly impacts the terminal ileum, any section of the gastrointestinal tract, from mouth to rectum, may be involved. Characteristic for the disease are inflammatory changes affecting individual bowel segments between which one usually finds healthy sections of bowel.

The inflammation can penetrate all the layers of the bowel wall, from the inner mucous membrane through the encircling muscular layer of the bowel wall and into the connective tissue that envelopes the bowel. The inflammatory process alters these tissue structures at increasing cost to the digestive functions of the bowel. Thus, the uptake or absorption of nutrients derived from the food and the release into the intestinal lumen of secretions crucial for the digestion of food are compromised. Complaints caused by disturbances of the metabolic functions are also described as **(extra)intestinal complications** and may affect both the digestive tract and other organs.

Even after the inflammation has subsided, scar tissue and thickening of the previously affected bowel segments may remain. This narrows the bowel lumen and hinders the transport of the intestinal contents.



What are the symptoms of Crohn's disease?

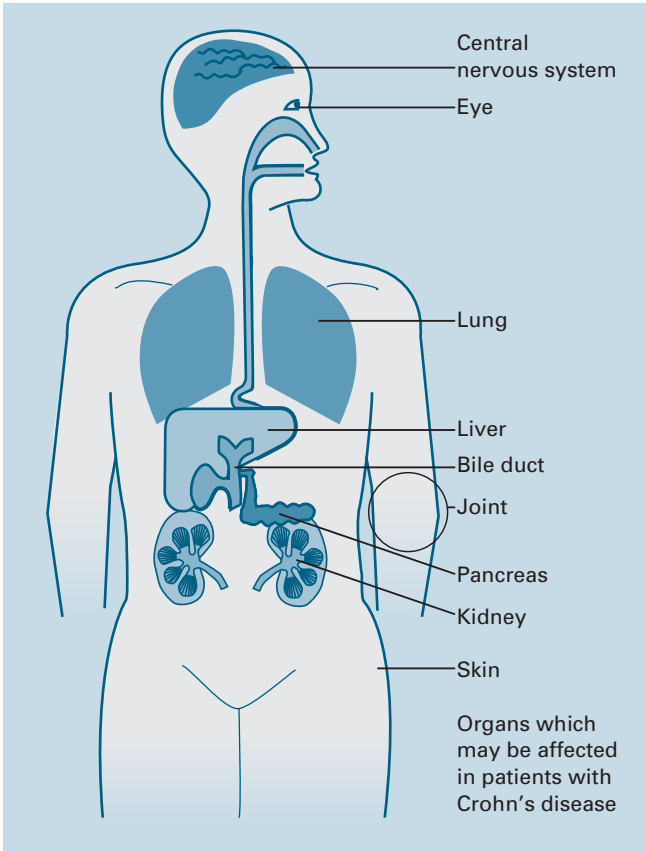
In many cases, Crohn's disease may develop slowly and symptoms may not be characteristic: Patients often report little more than unclear abdominal pains and increased diarrhea. Other patients, however, may experience a more severe disease onset with acute and very severe abdominal pain.

In addition to cramping abdominal pain, most Crohn's patients experience recurring episodes of diarrhea. Fever may also occur at irregular intervals and patients complain of weight loss and poor appetite (anorexia). Because patients' symptoms are often non-specific early in the course of the disease, establishing the correct diagnosis may be delayed. Evidence of an inflammatory bowel disease includes non-specific signs of inflammation in the blood (accelerated erythrocyte sedimentation rate [ESR], increased number of white blood cells, elevated concentrations of C-reactive protein [CRP] and, in some cases, reduced numbers of red blood cells) or detection of non-specific inflammatory markers in the stool (calprotectin, lactoferrin). The simultaneous occurrence of abdominal pain, diarrhea and fever with joint complaints, dermatitis (inflammation of the skin) or recurrent inflammation of the eyes may represent a sign of Crohn's disease. Fistulas in tissue surrounding the anus (anal fistulas) also point to Crohn's disease. Patients presenting with these patterns of symptoms can then be referred for a diagnostic ultrasound examination of the abdomen. This simple and painless examination rapidly yields further information: For example, evidence of thickening and inflammation of the bowel wall provides the first direct evidence of Crohn's disease.

Also complicating matters is the fact that the clinical course of Crohn's disease is not continuous: Disease activity occurs in flares interrupted by symptom-free intervals of varying length.

Crohn's disease and disorders of other organs

The effects of Crohn's disease are by no means restricted solely to the bowel. In fact, in nearly half of all Crohn's patients, other organs are involved, most commonly the joints (in about one-third of patients), followed by the skin (nearly 10%), the eyes (about 5%) and the biliary tract (about 1%). In some cases, this involvement of other organs in patients with Crohn's disease may



dominate the clinical picture and even mask the underlying disorder. On the other hand, the involvement of other organs may be more subtle and thus easily overlooked: It is, therefore, in the patient's own interest to be especially watchful for changes in the joints, skin or eyes and promptly inform his physician.

More rarely, there may be changes in the pancreas, whose secretions carry digestive enzymes into the bowel. Other patients may develop disorders of the respiratory tract, kidneys or nervous system as **extraintestinal manifestations** of Crohn's disease. While several organs may be affected simultaneously, some patients with Crohn's disease experience disease involvement of only one organ, which dominates the clinical picture. Clinical observations strongly suggest that these different extraintestinal manifestations have as a common cause a disturbance of the immune system.

On the other hand some of the manifestations associated with Crohn's disease may be caused by the medications used to treat this disorder (drug-induced **side effects**). The distinction between extraintestinal manifestations, complications (page 5) and drug side effects is important, as each requires different therapeutic measures.

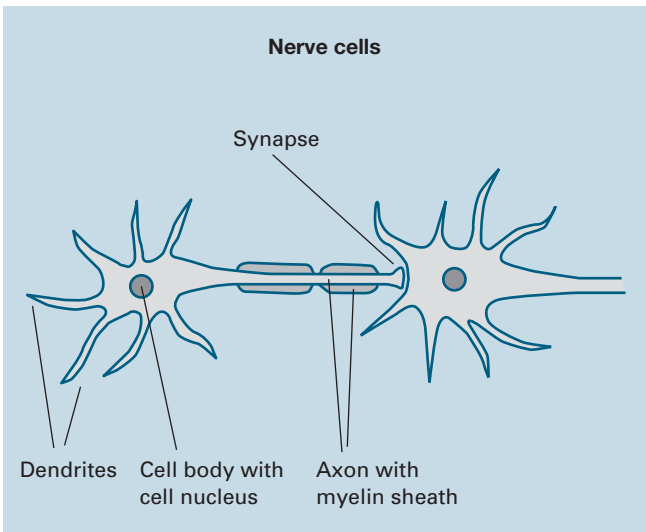
The role of the immune system

There is no single cause for Crohn's disease, no single factor that can be called *the* trigger for this disorder. The evidence, however, is mounting that a dysregulation of the immune system, based on a combination of genetic predisposition and environmental factors, is involved in its development. Thus, we speak of a multifactorial process. To date, researchers have identified over 70 "susceptibility genes" that are associated with Crohn's disease, though the exact mechanism by which they act is known for only a few of these. Still, based on our current understanding, it is possible to conclude that Crohn's disease is associated with a disturbance of the body's non-specific immune defenses. Its importance is underscored by the fact that the total surface area of the digestive tract, were all its folds to be laid out flat, would cover an area of 200–300 m². This large surface area is exposed to both the multitude of substances we take in through the mouth and the enormous number of bacteria which inhabit our bowel. Although their total mass is only about a kilogram, this corresponds to about a thousand trillion microbes, which belong to a number of different species. The intestinal mucosa serves as the boundary between the internal and external domains and is furnished with a large number of different types of immune cells. These cells are components of the defenses against invasion of the internal domain by dangerous foreign proteins and microorganisms. At the same time, it represents the interface that makes possible a "peaceful coexistence" with the intestinal bacteria. In Crohn's disease, this delicate balance is upset. There are larger numbers of defensive cells and they are activated, releasing excessive amounts of pro-inflammatory substances, such as cytokines (messenger substances), which ultimately destroy the mucosa and allow ulcerations and fistulas to form.

Nervous system

Reduced circulation and the blockage of small arteries in the brain can damage the nervous system. These changes may be due to an increase in the viscosity (resistance to flow) of the blood in response to inflammatory substances or to the loss of fluid in patients with diarrhea.

An inflamed segment of bowel or an overall shortening of the bowel due to surgical removal of diseased bowel loops can seriously limit the bowel's ability to absorb essential nutrients from the food and provide these to the organism. This affects the absorption of both the fat-soluble vitamins A, D, E and K, as well as that of the water-soluble vitamins of the B-group, such as vitamins B₆ und B₁₂. A deficiency of B vitamins is frequently associated with damage to the nervous system. Some Crohn's patients develop so-called polyneuropathies.



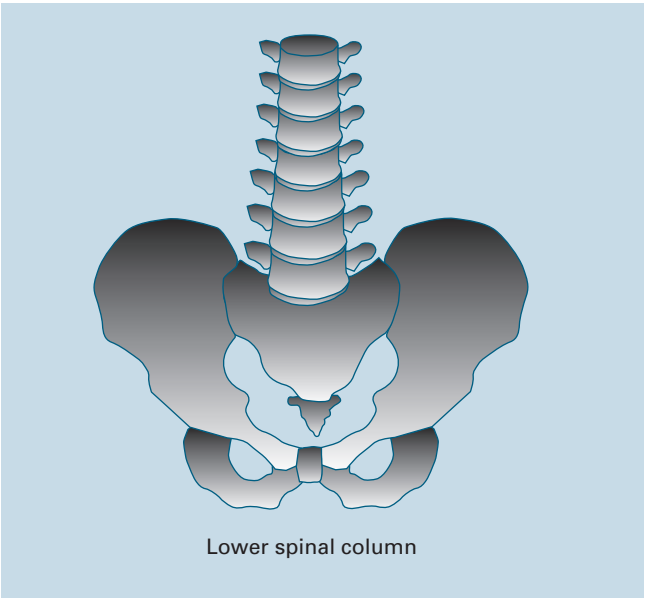
This refers to a condition in which there is a reduction in sensitivity within the region of the affected nerve, while at the same time there may be stabbing pains and a reduction in the normal muscle reflexes.

Patients with Crohn's disease suffer more frequently than the general population from other immunologically mediated diseases. Hence, inflammatory disorders of the brain, such as multiple sclerosis, may occur somewhat more frequently.

Disorders of the nervous system may also occur as medication side effects. For example, metronidazole, which is sometimes used in the treatment of Crohn's disease, by binding vitamin B, may cause polyneuropathy with unpleasant changes in the sensitivity of the hands and feet, or loss of muscle reflexes. If the drug is discontinued soon enough, however, these symptoms usually resolve. Another medication side effect of therapy with immunosuppressants, especially azathioprine, is the increased susceptibility to shingles, an infection with the herpes zoster virus, which is characterized by a painful rash in the area supplied by a specific nerve root. A very rare but serious side effect of treatment with immunosuppressants is the development of infections of the brain.

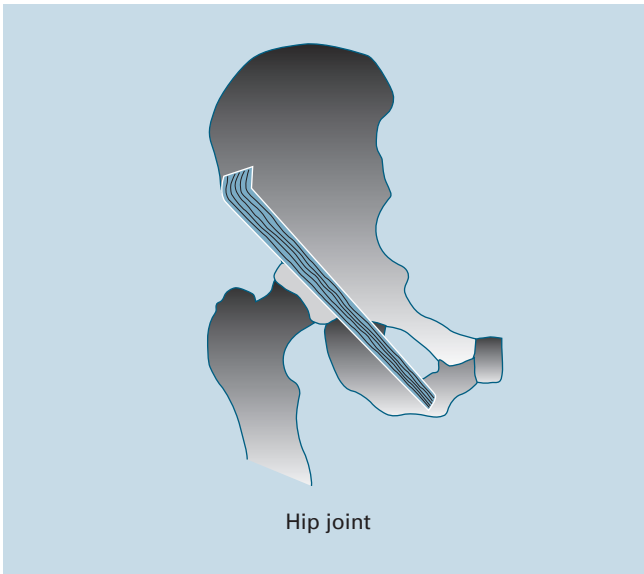
Joint problems

Patients with Crohn's disease often suffer from joint problems. Most common are simple arthralgias, or painful joints, without significant inflammation of the joints. Joints may, however, become inflamed, red and swollen (arthritis). There may be different patterns of joint involvement. For example, only a few large joints, such as the knees or elbows, may be affected. This frequently occurs during an acute Crohn's disease flare. The smaller, peripheral joints, such as in the fingers and toes, may also be involved: This involvement may be independent of the activity level of the underlying bowel inflammation. Some patients experience inflammation of the joints of the spinal column (axial arthritis, spondylitis).



Joint complaints may also be due to medication side effects, most commonly in patients treated with TNF antibodies.

The use of conventional antirheumatic medications, such as ibuprofen, naproxen or diclofenac, is problematic in Crohn's patients because these drugs may worsen the underlying disease or trigger a new disease flare. Other analgesics, such as acetaminophen or metamizole, are somewhat more suitable. Joint complaints occurring during a Crohn's disease flare, may improve in response to the treatment of the Crohn's disease itself, e.g. cortisone. In other cases, patients may require treatment with sulfasalazine or methotrexate. In refractory cases, especially when the spine is involved, therapy with TNF antibodies may be required.



Osteoporosis

Patients with Crohn's disease often suffer from reduced bone density. Also known as osteoporosis, this condition can increase the risk of fractures, especially of the spinal column. At greatest risk are patients with chronic disease activity and poor general nutritional status, as well as patients who have been treated for a long period with cortisone and those who have required surgery to remove significant lengths of their small bowel. Patients at risk are advised to take calcium and vitamin D as a prophylactic therapy to prevent osteoporosis. Patients with pronounced osteoporosis may benefit from treatment with one of the bisphosphonates, a group of medications which inhibit further bone destruction. Regular physical activity also contributes to increased stability of the bones.

Disorders of the eyes

Patients with Crohn's disease suffer from inflammatory changes of the eyes much more frequently than persons in the general population. The most common conditions include conjunctivitis (inflammation of the membrane lining the eyelids), partial or complete inflammation of the sclera (the white outer wall of the eye = episcleritis or scleritis), iridocyclitis (inflammation of the iris), uveitis (inflammation of the middle layer of the eye's outer wall) or retinitis (inflammation of the retina, the light-sensitive inner layer of the eye). Inflammation of the sclera or iris occurs most commonly in association with Crohn's disease, striking either at the first onset of the disease or at the time of a new disease flare. Patients experience a feeling of a foreign object in the eye, pain, light sensitivity and loss of visual acuity. These symptoms may occur individually or even simultaneously. Comprehensive management for this involvement of the eyes is a local therapy to target the patient's eye-related symptoms and effective therapy of the underlying inflammatory bowel disease.

It is crucial that both patients and their physicians consider the possibility of ocular involvement in association with Crohn's disease. This allows patients to be promptly referred for ophthalmological evaluation at the time of their first symptoms.

Skin changes

It is not uncommon for patients with Crohn's disease to develop inflammatory changes of the mucous membranes of the mouth. These changes, which occur in up to 10% of patients, are mostly sores, or aphthae, which develop on the basis of inflammatory processes typical for Crohn's disease as affect the bowel. Crohn's-typical inflammatory infiltrates can also affect the external skin, such as the area around the anus and external genital organs.

Also not rare are painful, reddish nodules (erythema nodosum) that arise on the front side of the lower legs. They usually, but not always, appear in association with a Crohn's disease flare. They often resolve in response to treatment, such as with cortisone preparations, aimed at the underlying disease. More rarely seen are purulent skin ulcerations (pyoderma gangraenosum) not caused by pathogenic bacteria ranging in size from only a few millimeters to several centimeters. These ulcerations are usually treated with cortisone preparations or immunosuppressants but may be quite resistant to therapy and ultimately require treatment with TNF antibodies.

Some changes in the skin relate to the loss or reduced uptake of vitamins and trace elements due to diarrhea with loss of blood and fluids. For example, anemia (reduced amounts of red blood cells and hemoglobin) may lead to glossitis, or inflammation of the tongue, which appears reddened and smooth. Eczema-like changes in the skin around the mouth can be due to a zinc deficiency. Zinc is an essential trace element for the body's immune defenses and a zinc deficiency can also lead

to delayed wound healing. Fungal infections can also more easily affect the skin due to the reduced immune defenses.

Some skin changes may be side effects of medications used to treat Crohn's disease. Most common are skin changes occurring in association with cortisone therapy. These changes include swelling and acne ("steroid acne"). With longer use, the skin may become thinner ("parchment skin") with a tendency toward bluish spots. Azathioprine increases sensitivity to light and increases the risk for non-melanoma skin cancer. TNF antibodies may cause eczema-like dermatitis (skin inflammation). Crohn's patients treated with these medications should take all recommended precautions to protect against sunlight and should see their dermatologist at least once a year.

Liver, biliary tract and pancreas

It happens more rarely that patients with Crohn's disease suffer from inflammatory involvement of the liver and biliary tract, including the gallbladder. Evidence for this involvement is the laboratory measurement of elevated levels of liver-specific enzymes in the blood.

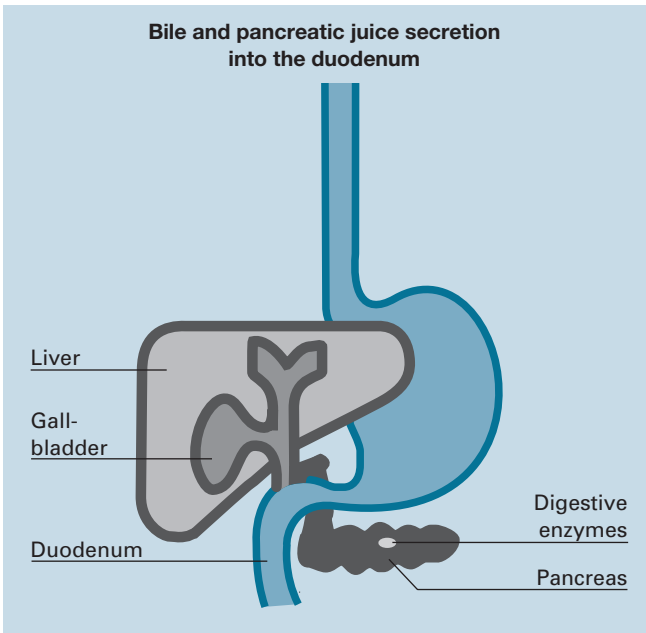
The liver tissue may show formation of granulomas, which are nodular accumulations of cells. These granulomas are also seen in the mucosal membrane of the bowel in Crohn's disease patients. When they occur in the liver, we speak of granulomatous hepatitis.

The biliary tract may be affected by a non-infectious inflammation leading ultimately to hardening and narrowing of the ducts in a disorder known as primary sclerosing cholangitis (PSC). The narrowing of the bile ducts can, by hindering the proper flow of bile, cause accumulation of the bile in the liver. If there is narrowing (stenosis) of the larger bile ducts, this can be visualized using a special endoscopic examination (endoscopic retrograde cholangiography = ERC) and, if needed, the narrowed sites can be dilated using a balloon or bridged using a small plastic tube (stent). In severe cases, patients with this disease can experience an increasing accumulation of bile in the liver, leading to increasing liver damage that may in some cases be so severe as to require liver transplantation. PSC is also associated with an increased risk of cancer of the bile ducts and cancer of the colon. Affected patients must therefore undergo regular monitoring examinations.

The pancreas plays a decisive role in digestion. It produces important digestive enzymes (amylase, lipase), which pass into the duodenum (uppermost segment of the small bowel) through a small duct. In some Crohn's patients, there is an increased concentration of these

enzymes. This increase in pancreatic enzymes in the blood is relatively unimportant so long as patients do not experience any complaints.

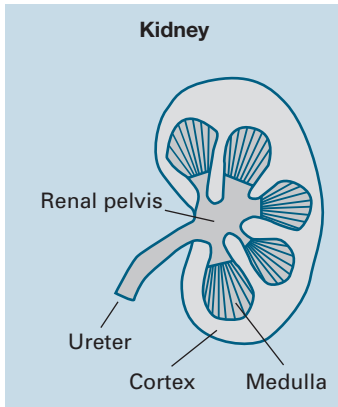
Some patients, however, develop pancreatitis or inflammation of the pancreas. This may represent a side effect of certain medications used to treat Crohn's disease. For example, about 2% of patients treated with azathioprine develop pancreatitis with abdominal pain. The inflammation of pancreas ordinarily resolves quickly once the medication has been discontinued. Other medications, such as mesalazine, sulfasalazine or cortisone preparations, are less frequently implicated as causes of pancreatitis.



Independent of their use of medications, patients with Crohn's disease have an increased risk of a special type of pancreas inflammation: autoimmune pancreatitis.

Kidney disorders

The risk of developing kidney stones (nephrolithiasis) is elevated in Crohn's patients. A major cause of this phenomenon appears to be the increased uptake of oxalic acid in damaged bowel segments. Kidney function may also be adversely affected by a condition known as amyloidosis, in which a certain type of protein is deposited in the kidney tissues. Similarly, the increased deposit of immune complexes along the renal ducts can impact kidney function. These patients experience an increased excretion of protein in the urine, due probably to damage to the membrane caused by inflammatory hormones, such as the tumor-necrosis factor (TNF), allowing passage of large protein molecules. The large fluid losses through the bowel can result in reduced concentrations and an altered balance of important electrolytes (sodium, potassium, bicarbonate). This mechanism can also promote the formation of kidney stones.



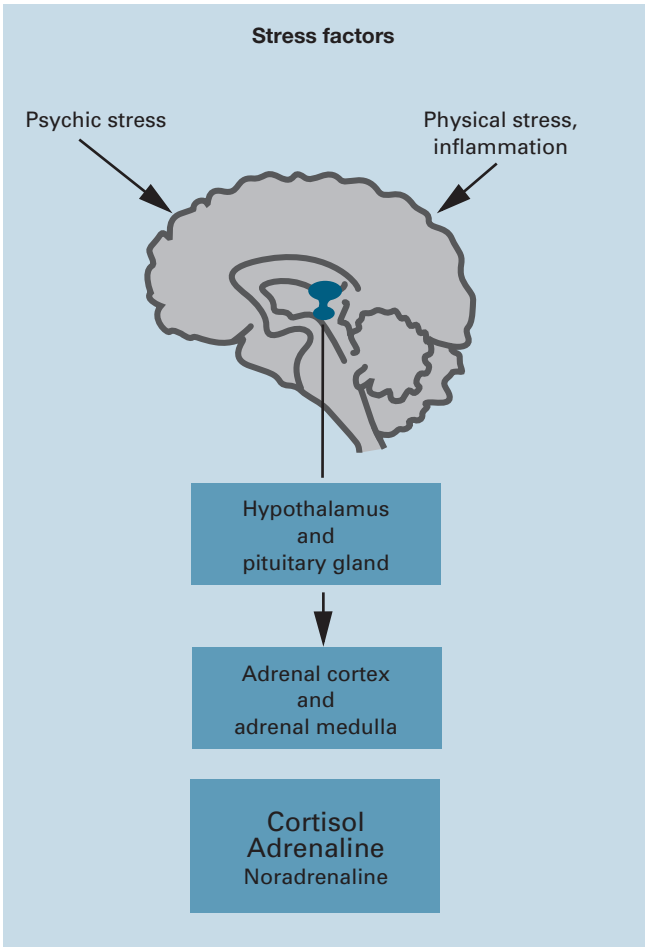
In very rare cases, patients treated for Crohn's disease may develop a type of nephritis, or inflammation of specific tissues in the kidney, the cause of which is believed to be an intolerance or allergy to the administered medications.

Respiratory tract

It appears very likely that immunological processes in the context of Crohn's disease may also cause changes in the respiratory tract. Many patients have at least mildly compromised respiratory function. The effects, however, may be quite variable. For example, in some patients there is inflammatory change or narrowing of the trachea and bronchi. In a few cases, there may be an allergy-like inflammation of the alveoli (alveolitis). The pleural membrane, which envelopes the lungs, may also be involved (pleurisy). Because these conditions occur rarely in association with Crohn's disease, it has not yet been possible to identify any clear correlation with either the disease activity or duration. Complicating the matter still further is the fact that some of the medications used to treat Crohn's disease are known to cause allergic or inflammatory reactions in the lungs. It is possible that patients whose respiratory function has already been adversely affected by other disorders are at especial risk for these complications.

Psychological effects

It is quite understandable that patients suffering an acute Crohn's disease flare are subject to increased psychological stress. This can, in turn, negatively impact the course of the disease. In some cases, stress or burdensome life situations, such as separation from a partner or career pressure can worsen the course of Crohn's disease. Although the exact mechanisms responsible for these observations remain unclear, it is known that there is extensive interaction between the brain and the immune system. These interactions are mediated by the vegetative nervous system as well as by regulatory hormones secreted by the pituitary gland. Conversely, the immune system affects the brain through messenger molecules, such as the cytokines. Thus, a broad basis exists for mutual interactions of psyche and immune system. Although psychic factors can certainly exert an influence over the clinical course of Crohn's disease, there is no longer any speculation that Crohn's disease is triggered by psychic factors alone. Still, psychological problems may so dominate the clinical picture that patients may require a specific psychotherapeutic treatment.



Coagulation and circulation

Patients with Crohn's disease exhibit an increased tendency of the blood to coagulate, or clot. This puts them an increased risk of developing blood clots in their venous circulation, which may lead to thromboses or embolisms. Frequently, these clots form in the veins of the leg and, if they become dislodged, may be carried with the circulation into the lung, resulting in a potentially life-threatening pulmonary embolism. Crohn's patients are at a higher risk than the general population for developing thromboses and embolisms.

Underlying this increased risk are the inflammatory processes that increase the tendency of the blood to coagulate. Thus, patients in an acute disease flare are at higher risk, especially those who require hospitalization and who remain in bed or walk very little. To counter this risk, your treating physician may prescribe certain medications, such as heparin or warfarin (Coumadin, Marcumar), whose use requires specific precautions. The majority of Crohn's patients, however, do not routinely require any medication to prevent blood clots.

The risk of developing circulatory problems involving the arterial venous system, such as coronary artery disease (CAD) leading to a heart attack, circulation problems in the legs, or stroke is not increased in Crohn's disease patients. Crohn's patients, who smoke, however, are at increased risk for these disorders as a result of their tobacco consumption.

Cancer risk in Crohn's disease

A long history of Crohn's disease involving the colon (over 10 years) is associated with an increased risk of developing cancer of the colon. Compared with the general population, this risk is, on average, doubled. For this reason, Crohn's patients with extensive disease involvement of the colon should undergo colonoscopy every one to two years once they have reached eight years after first onset of symptoms. This is the best way to discover any malignancy of the colon at an early stage, when it can often be completely cured with surgery. There is evidence that regular treatment with sulfasalazine or 5-aminosalicylic acid may reduce the risk of colon cancer.

Patients with Crohn's disease also have an increased risk for cancer of the small bowel. Because this kind of cancer is very rare, however, even with this increased risk very few Crohn's patients will be affected. Therefore, in contrast to cancer of the colon, there are no recommendations for measures to screen for cancer of the small bowel.

Patients with Crohn's disease and inflammation of the bile ducts (primary sclerosing cholangitis) have an increased risk of cancer in both the bile ducts and the colon. Hence, these patients benefit from regular preventive screenings.

Crohn's patients are also at a moderately increased risk for tumors outside the gastrointestinal tract. These malignancies include non-melanoma skin cancer and cancer of the lymph nodes. This increased risk is due in large part to the immunosuppressant medications used in the treatment of Crohn's disease. The skin

cancer risk can be managed with careful protection against sunlight and regular visits to the dermatologist. Cancer of the lymph nodes is fairly rare, hence, despite the moderately increased risk, the absolute risk remains very low and should not be grounds for worry.

Living with Crohn's disease

Inflammatory bowel diseases, of which Crohn's disease and ulcerative colitis are the most common types, are disease entities whose causes have not yet been completely understood. Thus, treatments that get at the root cause of these disorders remain unavailable. The therapeutic alliance between the patient and his physician is determined by, on one hand, the patient's subjective experience of his illness, and, on the other, by the physician's knowledge and experience. It is not unusual that the physician's objective estimation of the disease and its severity differs from the patient's subjective perception. Also, each patient will experience phases of strength, in which the illness is better tolerated and accepted than in more stressful periods during which the capability to manage the situation may be completely lost.

Until the day when reliable, causal methods for curing the disease become available, therapy will remain limited to lessening symptoms and preventing or treating complications. Beginning with sensible nutrition and a large number of drugs with a variety of pharmacological actions, the available spectrum of successful treatment methods also includes the option of psychological therapies and surgery. The close cooperation of physician and patient will help determine which conservative (non-surgical) methods are appropriate and how they may be combined; it will also set the stage for discussing the surgical option, when – and if – this becomes unavoidable.

An especially important resource are the many self-help groups that have been formed to help patients with Crohn's disease and their families. These provide a venue for people with very similar problems to meet

and exchange experiences. They also help in communicating useful recommendations on correct behavior, nutrition and diet, and much more. Most importantly, they provide understanding and support for patients and families dealing with the lifelong challenge of Crohn's disease.

Physician, family and self-help group are integral parts of the immediate social environment of the patient with Crohn's disease. Comprehensive discussions and cooperatively developed strategies for dealing with both major and day-to-day problems will not only help the Crohn's patient to accept his chronic illness but also promote a better understanding of the disease and its challenges among persons making up the patient's social environment.

Crohn's disease and pregnancy

Crohn's disease is a disorder that often strikes young adults. This is a time during which many people start, or at least begin to plan, their families. Women suffering from Crohn's disease should try to plan a pregnancy to fall during a period of low disease activity (remission). Regardless of the timing of a potential pregnancy, however, the question remains of exactly what effects pregnancy has on Crohn's disease and, conversely, how Crohn's disease affects a woman's ability to conceive and carry a child.

Pregnancy can have both favorable and unfavorable effects on the clinical course of Crohn's disease. Among pregnant Crohn's patients, about one-third, each, reports improvement, worsening or no change in terms of their bowel disease. The impact of Crohn's disease on pregnancy depends, at least in part, on the current level of Crohn's disease activity. To start with a piece of good news: Pregnant women with Crohn's disease need not, as a rule, fear serious problems. In particular, there is no increase in the risk for miscarriage or for congenital defects in the child. There is, however, an increased risk for premature delivery and for low birth weight in the child, especially when Crohn's disease is active. For this reason, as stated above, it is recommended, whenever possible, that pregnancy be planned for a period in which patients' Crohn's disease is in remission.

One important question is: What medications are allowed in women with Crohn's disease who are, or hope to become, pregnant? Many package inserts alert to the risks of a certain medication in pregnancy or when nursing. On the other hand, it is important that Crohn's disease does not get out of control during pregnancy,

whether actual or planned. Hence, the continued use of medication may be necessary, requiring a careful risk-to-benefit review. Least worrisome are cortisone preparations and mesalazine. Methotrexate is absolutely contraindicated in women who are, or plan to become, pregnant. Most commonly, attention focuses on a strict risk-to-benefit assessment of azathioprine, a medication prescribed to many patients for long-term remission maintenance. Numerous observations have failed to provide evidence that the use of azathioprine in pregnant women is associated with any negative effects on either the course of the pregnancy or the development of the fetus. Similar observations, though fewer in number, have been reported for treatment with TNF antibodies. Naturally, there are many other factors involved in the use of medication during pregnancy, especially during its early and late phases, that cannot be discussed in detail here. Most important is the close cooperation between the gynecologist assisting with a woman's reproductive needs and the internist or gastroenterologist managing her Crohn's disease: This helps identify any problems early and facilitates their being solved promptly and in an interdisciplinary manner.

Nutrition in Crohn's disease

There is no single “Crohn’s diet” that best serves all patients with Crohn’s disease. Still, there are many recommendations that are intended to help patients avoid nutrition pitfalls. For example, foods that cause excessive flatulence should not be part of a Crohn’s patient’s menu. Foods rich in dietary fiber support regular bowel function and a normal intestinal flora. Patients with scar tissue or inflammation causing a narrowing (stenosis) of the bowel, however, should exercise caution with respect to dietary fiber and adhere to a diet that is low in fiber.

Patients and their physicians should be aware that nutritional deficits and nutrient deficiencies can occur during a period of acute intestinal inflammation. The consequences of nutrient deficiency, especially for protein, fats, electrolytes, vitamins and trace elements may set in and, depending on the patient’s acute or chronic disease status, have a variety of causes:

Protein deficiency may occur due to:

- consuming an unbalanced diet or fasting due to fear of symptoms;
- inflammation of segments of the bowel that prevents adequate absorption of nutrients;
- loss from the bowel of inflammation-related secretions with high protein-content;
- increased loss of protein with the urine due to kidney damage.

Blood loss is the main cause of **iron deficiency**. However, it may also be caused by reduced iron intake due to failure to eat foods rich in iron, as may occur in patients with abdominal pains, or to reduced absorption of iron as a result of the inflammatory bowel disease itself.

Because iron is an essential component of hemoglobin, the oxygen-carrying molecule found in red blood cells, iron deficiency can lead to anemia. Anemia may also be due to changes in iron metabolism as may occur in patients with any chronic active inflammatory process.

Vitamin deficiencies, especially deficiencies of fat-soluble vitamins (A, D, E, K) may be due to an unbalanced, nutrient-deficient diet in patients with chronic disease activity, as well as to wide-spread small bowel inflammation or extensive surgical removal of segments of the small bowel. Of particular importance are deficiencies of vitamins D (risk of osteoporosis) and B₁₂ (anemia).

Water- and electrolyte imbalances may occur due to the loss of large amounts of fluid in patients with watery diarrhea. Electrolytes such as sodium, potassium, calcium and chloride are dissolved in every body fluid and their balance may be impacted by large fluid losses. These losses can be replaced by changes to the diet or supplementation of electrolytes in the form of tablets or electrolyte drinks.

Trace elements such as magnesium, copper, selenium and zinc play important roles in the function of many organs. The amounts of these substances present in the body can be monitored at a patient's yearly check-up and can be replaced pharmaceutically if needed.

Pharmacological treatment of Crohn's disease

Drugs are used both in the treatment of acute disease flares (acute phase therapy) and to protect against relapses (remission maintenance).

“Cortisone” (more correctly, corticosteroids)

The corticosteroids (popularly known as “cortisone”) represent some of the most important drugs available for treating Crohn's disease. They include agents such as prednisone, prednisolone and methylprednisolone. Patients, whose disease affects only the small bowel and those with a combination of small and large bowel involvement, generally respond well to corticosteroids. They are less effective in patients with Crohn's disease affecting only the colon. For treatment of acute disease, corticosteroids must be given at sufficiently high doses (e.g. prednisolone is dosed at about 1 mg per kilogram of body weight per day). If the disease activity declines, the corticosteroid dose can be slowly tapered and the agent can be completely discontinued after two to three months.

Budesonide

Corticosteroids are highly effective but can have serious adverse effects. For this reason, researchers have attempted to develop new types of corticosteroids that preserve this high efficacy but have fewer side effects. Of these new topical (predominantly locally acting) corticosteroids, budesonide has established itself over the past few years.

Budesonide, which can be given either orally as a capsule or rectally as an enema or rectal foam, acts directly on the inflammation of the intestinal mucosa. It is also absorbed there and transported to the liver. Unlike con-

ventional corticosteroids, budesonide is metabolized in the liver so completely (over 90%) that only a small amount is distributed through the body, where it can cause side effects. A number of large studies have shown that budesonide, when compared to older systemically active corticosteroids, exhibits only slightly lower efficacy with a significantly lower rate of side effects. Budesonide, however, should not be used in cases of very severe disease activity, in patients with extensive extraintestinal involvement of other organs, and in patients in whom the esophagus, stomach or duodenum are affected, since budesonide is not sufficiently effective at these sites.

Salazosulfapyridine

Salazosulfapyridine plays only a subordinate role in the treatment of Crohn's disease today. Its use is mainly restricted to joint involvement in patients with Crohn's disease.

Mesalazine/5-Aminosalicylic acid (5-ASA)

Mesalazine has superseded salazosulfapyridine in the treatment of Crohn's disease. Mesalazine can be used to treat a mild Crohn's disease flare, especially in the cases in which the terminal ileum and colon are affected. Mesalazine can also be used to protect against a recurrent Crohn's disease flare. One advantage of this substance is its good tolerability. Mesalazine can be given in the form of tablets, enemas, suppositories or rectal foam.

Azathioprine

A very effective medication for the long-term treatment of Crohn's disease is azathioprine, which is especially suitable for treating corticosteroid-dependent patients and those whose disease is resistant to corticosteroids. Azathioprine is also effective for preventing disease

relapse (remission maintenance). It is more effective than mesalazine but, due to its inhibitory effects on the immune system, requires closer monitoring of patients.

Methotrexate

An alternative for patients who do not tolerate azathioprine or, in cases, when azathioprine fails, methotrexate can be prescribed. Methotrexate is given once a week, either as tablets or as an intramuscular injection. Methotrexate cannot be used in cases of planned or existing pregnancy.

Anti-TNF- α antibodies

The so-called tumor necrosis factor- α (TNF- α) plays an important role in the inflammatory process in inflammatory bowel diseases. Anti-TNF- α antibodies suppress the immune system and inhibit inflammation. Currently available are two different preparations that can either be given as an infusion or injected subcutaneously. Anti-TNF- α antibodies can be given to patients with Crohn's disease after other standard therapeutic measures have failed. In some patients, these antibodies lead to a rapid drop in disease activity. This is also true in part for patients with fistulae. The regular, repeated administration of these antibodies can prevent disease recurrence in at least one part of patients.

Treatment of Crohn's disease aims first at resolving the acute inflammation in the most effective way possible. Beyond this, therapy aims at lengthening periods of remission and reducing as far as possible the risk of recurring acute disease flares. This requires a comprehensive regimen of pharmacological therapy, adapted diet and nutrition, and, when needed, psychological support.

Close cooperation between physician and patient makes it possible to achieve a high degree of control over disease activity in Crohn's disease. This allows Crohn's patients to live quite normal lives. By keeping symptoms to a minimum, Crohn's patients can expect to achieve a very satisfactory quality of life.

Glossary

Absorption: uptake of nutrients through the skin or mucous membrane, or from tissues into the blood or lymphatic system

5-Aminosalicylic acid (5-ASA, mesalazine): chemical substance (pharmaceutical) whose properties reduce inflammation and promote mucosal healing. Because of its high tolerability, mesalazine is especially used in ulcerative colitis for treating acute disease flares and for long-term remission maintenance

Amyloidosis: accumulation of protein in the connective tissue with resulting disturbance of metabolism

Arthritis: inflammatory joint disorder

Azathioprine: pharmaceutical in the group of immunosuppressants used for the long-term treatment of Crohn's disease

Budesonide: corticosteroid pharmaceutical with anti-inflammatory properties (similar to cortisone) but significantly fewer side effects than conventional corticosteroids

Calprotectin: a protein found in white blood cells. Its presence in stool is a marker for intestinal inflammation

Causal treatment: therapy aimed at the root causes of a disease

Cholangitis: inflammation of the bile ducts

Conjunctivitis: inflammation of the conjunctiva (an outer layer of tissue in the eye)

Conservative therapy: non-surgical treatment form (drugs, diet, physical therapy etc.)

“Cortisone”: popular term for various members of a group of pharmaceuticals (glucocorticoids or corticosteroids) derived from the hormone produced by the adrenal cortex. Because of its anti-inflammatory effects, it is used in treating Crohn’s disease with high disease activity

Crohn (Burril B.): American gastroenterologist (1884–1983) who first described *Ileitis regionalis* as a distinct disease entity (Crohn’s disease)

CRP: C-reactive protein: an inflammation marker in the blood

Cytokines: messenger substances in inflammatory processes

Embolism: occlusion of a blood vessel caused by a blood clot that has broken free and been carried by the circulation from another vessel (for example, pulmonary embolism is the lodging of a blood clot in the lungs from vessels in the legs)

Enzymes: proteins that act as biocatalysts in accelerating chemical reactions

Episcleritis: inflammation of the connective tissue between the sclera and conjunctiva of the eyes

Erythema nodosum: acute inflammatory skin disease of the subcutaneous fat tissue

Erythrocyte sedimentation rate (ESR): the rate at which red blood cells in treated blood sink in response to gravity (evidence for possible inflammation if elevated)

Fistula: an abnormal tube-like passage between a diseased hollow organ (e.g. the bowel) and another organ (e.g. bladder) or the body surface

Granuloma: nodular growth typically occurring in tissue as a response to an inflammatory process

Ileitis terminalis: “Terminal ileitis” described an inflammation at the final segment of the small bowel. It is an alternate term for regional Crohn’s disease

Immunosuppressants: any of a group of pharmaceutical agents that inhibit the function of the immune system. They reduce exaggerated immune reactions and inflammation, but also inhibit the body’s normal defense reactions

Immune system: complex system in vertebrates that protects the body against invading foreign substances and organisms

Iridocyclitis: inflammation of the eyes affecting the iris and ciliary body (middle layer of tissue in the eye)

Lactoferrin: a protein found in white blood cells. Its presence in stool is a marker for intestinal inflammation

Lesion: site of damage or injury to tissue

Lumen, intestinal: the interior space of the bowel through which the intestinal contents are transported and nutrients are absorbed into the body

Mesalazine: see **5-Aminosalicylic acid**

Methotrexate: medication in the group of the immunosuppressants

Nephrolithiasis: kidney stone disease

Oligoarthritis: inflammation of two to four joints simultaneously

Pancreatitis: inflammation of the pancreas

Polyneuropathy: disease of the peripheral nerves

PSC: primary sclerosing cholangitis (special form of bile duct inflammation)

Psyche: the mind or spirit

Retinitis: inflammation of the innermost tissue layer of the eye

Salazosulfapyridine: compound formed from 5-aminosalicylic acid and sulfapyridine

Secretion: release of fluid from an organ or of molecules from cells

Scleritis: inflammation of the sclera, the white outer covering of the eye

Stenosis: narrowing of a hollow organ, such as the bowel

Subcutaneous: beneath the skin

Thrombosis: formation of a blood clot within a vessel, usually in a vein of the leg

TNF: “tumor necrosis factor” (historical name): important mediator (messenger substance) of inflammation (cytokine)

Uveitis: inflammation of the middle layer of the covering of the eye

FALK FOUNDATION e.V.



Leinenweberstr. 5
79108 Freiburg
Germany

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