Ulcerative colitis – Crohn's disease

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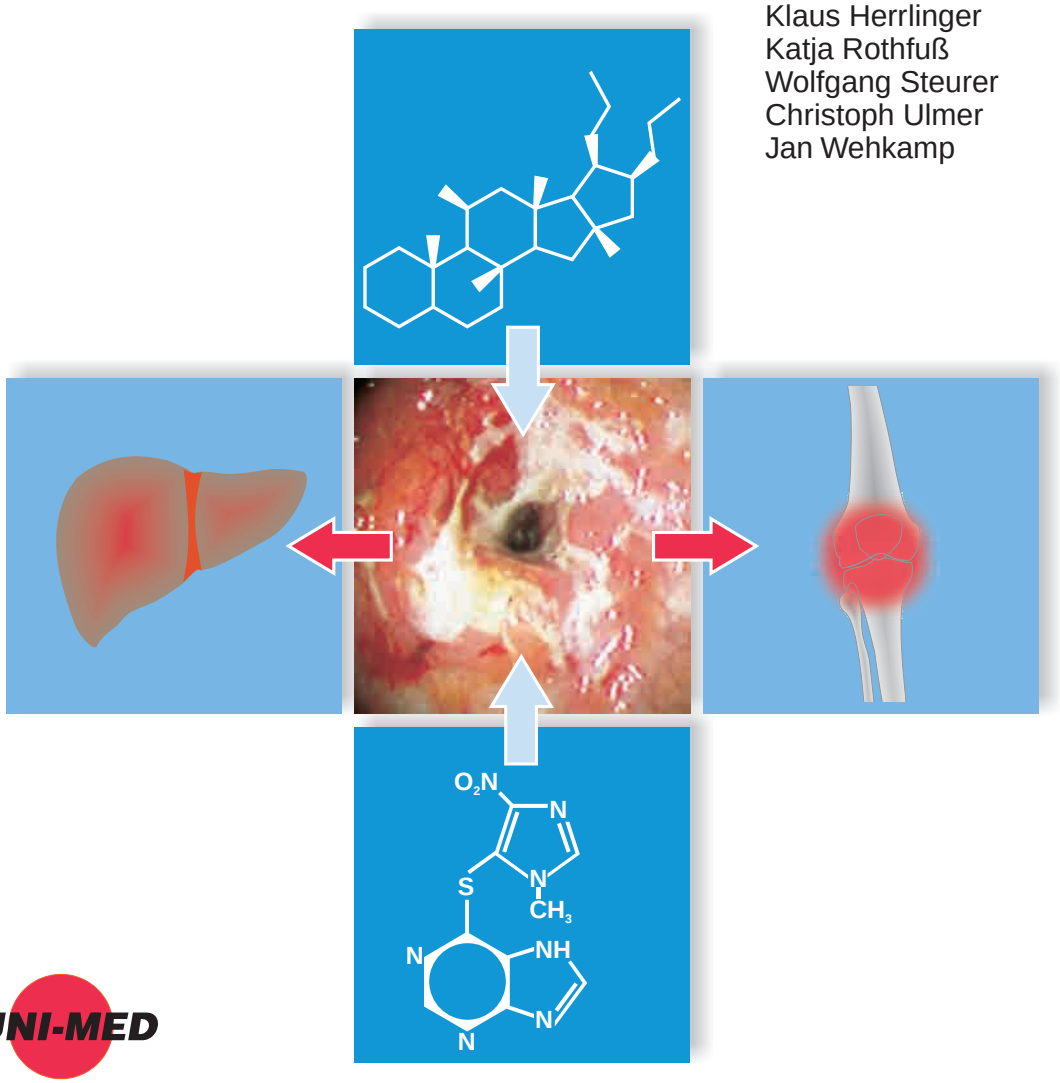

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Preface and acknowledgements

Ulcerative colitis and Crohn's disease are inflammatory bowel diseases that mainly occur in the second and third decade of life. As the prevalence is 1:700 to 1:1500, these two diseases are not uncommon but most doctors only care for a few patients with this diagnosis. There is consequently only limited experience in the management of these patients. This perhaps also explains why the diagnosis is often delayed. Moreover, the treatment strategies are becoming increasingly complex with the new but now well-established antibody therapies.

This book aims to provide the necessary knowledge about inflammatory bowel disease in a compact form. The sections on pathophysiology, diagnostic investigation and current therapy have been revised by the experts to include the latest developments. Special value has been attached to evidence-based therapy, which is based on numerous controlled trials and meta-analyses. A separate chapter is devoted to the extraintestinal manifestations that often pose problems for the physician. Lastly, new surgical treatments for inflammatory bowel disease are reviewed.

The volume is not intended as a complete reference work but as a compact source of information for relevant questions. I would like to warmly thank all co-authors and the publishers for their excellent cooperation. I very much hope that this volume will prove to be of use to a great many doctors and above all patients.

Stuttgart, June 2017 *Eduard F. Stange*

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Contents

Epidemiology, aetiology and pathophysiology

1. Epidemiology, aetiology and pathophysiology

Crohn's disease (CD) and ulcerative colitis (UC) are relapsing-remitting inflammatory bowel diseases. Even though the aetiology of these conditions is not yet fully understood, recent years have nevertheless seen discoveries about essential and important aspects of their pathogenesis.

The current concept is based on the finding that both diseases arise from interplay between genetic factors and environmental influences. The composition of the intestinal flora and especially primary disorders of innate immunity in the form of a barrier defect in relation to normal bowel bacteria are also significant (☞ Figure 1.1).

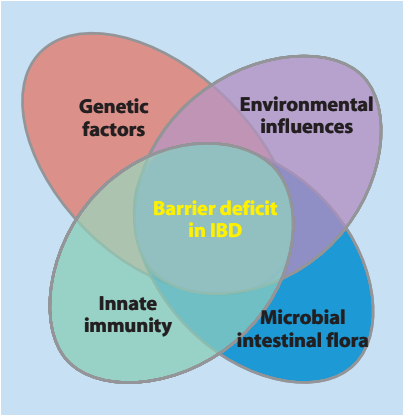

Figure 1.1: Factors involved in the occurrence of inflammatory bowel disease (IBD).

1.1. Epidemiology

A large number of epidemiological studies recorded the incidence and prevalence of Crohn's disease and ulcerative colitis in different countries and their development over the last few decades. The incidence describes the number of new occurrences of the disease per 100,000 of the population per year while the prevalence defines how many per 100,000 of the population are affected by a specific illness (in this instance, inflammatory bowel disease) at a given time. The worldwide distribution of Crohn's disease and ulcerative colitis makes it possible to draw conclusions on aspects that are of significance for the pathogenesis.

Table 1.1 provides a tabulated summary of a recent systematic review of the worldwide incidence and prevalence of inflammatory bowel disease. When viewed as a whole, the peak incidence of Crohn's disease is 20.2 (North America) and the peak incidence of ulcerative colitis is 24.3 (Europe). The incidence of ulcerative colitis in Europe is roughly twice that of Crohn's disease. The prevalence of Crohn's disease is a maximum of 322 in Europe (=1/311), while that of ulcerative colitis is as high as 505 (=1/198).

Interestingly, the incidence of both types of inflammatory bowel disease in Europe and America displays a clear north-south divide with higher incidences in northern countries and lower incidences in southern countries. In Asia, Africa and Latin America, the incidences of ulcerative colitis and Crohn's disease are, moreover, much lower than in North America and Europe. This initially suggested that ethnic background, mediated by genetic factors, plays a certain role in the pathogenesis of the two diseases. Migration studies were able to show, for example, that immigrants from countries with a low incidence of inflammatory bowel disease who moved to a country with a high incidence initially kept their low risk of developing ulcerative colitis or Crohn's disease. Over time, however, the risk of disease came to match the region to which they had emigrated. As it was also simultaneously noted that the incidence in cities is

Region	CD		UC	
	Incidence	Prevalence	Incidence	Prevalence
Europe	0.3 to 12.7	0.6 to 322	0.6 to 24.3	4.9 to 505
North America	0 to 20.2	16.7 to 318.5	0 to 19.2	37.5 to 248.6
South America	0 to 2.6	15	1.2 to 4	76.1
Asia/Middle East	0.1 to 5	0.9 to 67.9	0.1 to 6.3	4.9 to 168.3

Table 1.1: Incidence and prevalence (based on Molodecky et al.)

higher than in the surrounding rural regions, it may not just be the ethnic origin or genetics that is of relevance to the pathogenesis. The occurrence of Crohn's disease and ulcerative colitis is probably at least equally mediated by environmental influences.

Several studies showed that the incidence of both types of inflammatory bowel disease has risen over the last decades nearly everywhere. This may be due to a simultaneous change in lifestyle and environmental factors but not to genetic factors. Alternatively, heightened awareness of doctors about the two diseases and increasingly better diagnostic possibilities could, however, also be responsible for this. Lastly, it is also conceivable that given the improved survival of a predisposed cohort in childhood, e.g. through antibiotics in the presence of a non-lethal defect in the innate immune system the later occurrence of the disease is rendered more likely and thus the incidence increases.

In principle, the two types of inflammatory bowel disease can occur at any age even though most illnesses manifest themselves in the second or third decade of life. Crohn's disease tends to affect younger patients than ulcerative colitis and develops somewhat more often in females, while ulcerative colitis does not show any sex predilection. Lastly, several studies have shown that life expectancy in patients with inflammatory bowel disease is not shortened to any significant extent.

1.2. Environmental influences and risk factors

Environmental influences and risk factors can influence the occurrence and course of inflammatory bowel disease. In particular, smoking and high hygiene standards in the home are important here but others such as the use of antibiotics, oral contraceptives, duration of breast-feeding and appendectomy can influence Crohn's disease and ulcerative colitis (☞ Table 1.2).

1.2.1. Smoking

Smoking is the risk factor that has been best studied. A meta-analysis found a two-fold increase in risk for smokers for developing Crohn's disease. In addition, it was found that patients who were smokers and had Crohn's disease not only experience more frequent flare-ups, but the number of surgical interventions and need for steroids and immunosuppressants are increased in these patients. Last but not least, there was also found to be reduced quality of life in these patients. Paradoxically, the relationship in ulcerative colitis is exactly the reverse – here, smoking has a certain protective effect: the risk for non-smokers in these patients is 2.9 times higher compared with smokers, and many patients are ex-smokers with disease onset after they stopped smoking. In each case, passive smoking appears to have a similar but lower effect

	Crohn's disease	Ulcerative colitis
Nicotine	• Increased risk of disease • Increased risk of relapse • Increased need for surgical intervention • Increased requirement for steroids and immunosuppressants • Decreased quality of life	• Protective effect
Measles virus Mycobacteria	Disputed	
High hygiene standards (in childhood) Antibiotics	Increased risk of disease	
Contraceptives	Questionable positive association	Questionable positive association
Appendectomy	Disputed	Marked negative association
Breast-feeding	Probably a protective effect	Probably a protective effect

Table 1.2: Environmental influences and risk factors in inflammatory bowel disease.

on the two diseases. Nevertheless, patients with ulcerative colitis should also be advised not to smoke because of the serious complications arising from smoking. It has not yet been established with certainty how exactly smoking or nicotine acts in inflammatory bowel disease.

1.2.2. Mycobacteria, other microorganisms and infections

The role of mycobacteria in Crohn's disease is a subject of discussion; in ulcerative colitis, they probably do not play any role. Although several studies have shown that *Mycobacterium paratuberculosis*, in particular, (a microorganism found in cattle), can be detected in the bowel of Crohn's disease patients to a disproportionately common extent, other studies were unable to confirm this; furthermore, the microorganism could not be detected in the majority of patients. In addition, a large study on the therapeutic use of tuberculostatics had a negative outcome. Thus, the significance of mycobacteria in the pathogenesis of Crohn's disease is rather doubtful. As other microorganisms such as Listeria, *E. coli*, Streptococci, adenoviruses and cytomegalovirus along with other infections were associated with inflammatory bowel disease, one particular species does not therefore appear to be relevant for the pathogenesis.

1.2.3. Hygiene and antibiotics

Frequent gastrointestinal infections in early childhood are negatively associated with Crohn's disease; in this case, therefore, they appear to have a protective effect. This has been confirmed by the observation that high hygiene standards in the home are positively associated with the development of Crohn's disease. Conversely, poor hygiene standards appear to protect against Crohn's disease. It is suspected that early bowel infections positively support the development of the innate and adaptive immune system. If the body does not have to deal with pathogenic and non-pathogenic microorganisms due to excessive hygiene standards especially in childhood, this possibly results in an excessive immune response in relation to harmless infections and even to chronic inflammation.

On the other hand, the frequency of the use of antibiotics in childhood is increased in patients with Crohn's disease but not in ulcerative colitis, with a relative risk of 3.4 compared with controls. It is speculated that this has a long-term effect on the bacterial flora and thus the risk of Crohn's disease increases. On the other hand, there could also be a predisposition to infections: the 3- to 5-fold higher frequency of pneumonias in early childhood (up to 5 years) in patients who go on to develop Crohn's disease fits in with this.

1.2.4. Contraceptives

A meta-analysis from as early as 1995 showed that women on oral contraceptives have 1.4 times the risk of Crohn's disease and 1.3 times the risk of ulcerative colitis. Other case studies even found a much higher risk for the development of the two types of inflammatory bowel disease with the use of the Pill. Even though not all studies found an association between the Pill and inflammatory bowel disease, this is considered to be definite for Crohn's disease, at least in part. By contrast, postmenopausal hormone administration tends to be associated more with ulcerative colitis.

1.2.5. Appendectomy

A meta-analysis from the year 2000 summarising a total of 13 case-control studies showed that appendectomy reduces the risk of ulcerative colitis by 69%. It was concluded from this that removal of the appendix has a protective effect in relation to the development of ulcerative colitis. However, this clear association does not prove a causal association. The data on Crohn's disease are conflicting.

1.2.6. Breast-feeding

A sufficiently long period of breast-feeding appears to protect the newborn child from inflammatory bowel disease, at least to a certain extent, probably due to the improvement in oral tolerance for microbiota.

1.2.7. Other risk factors

Many other risk factors appear to be more or less associated with Crohn's disease or ulcerative colitis. In particular, eating habits, such as intake of crystallised sugar, a high-fibre diet, unsaturated fatty acids, vitamin B_6, chocolate and cola were associated with inflammatory bowel disease in individual studies. Physical activity and sport halved the risk of Crohn's disease, while non-steroidal

anti-inflammatory drugs slightly increased the frequency of occurrence of inflammatory bowel disease. Overall, it is surprising that despite the known great importance of environmental factors the data are much less conclusive compared with genetics.

1.3. Genetics

The evidence for a strong genetic component in the occurrence of disease is disputed for inflammatory bowel disease. Concordance among monozygotic twins is 20-50% for Crohn's disease, and only 0-7% among dizygotic twins. The corresponding figures for ulcerative colitis are 14-19% and 0-5% and somewhat lower indicating a weaker role of genetics in this disease. The relative risk of siblings of patients with inflammatory bowel disease is 30-40 (Crohn's disease) and 10-20 (ulcerative colitis). Interestingly, the risk of ulcerative colitis is also increased in siblings of patients with Crohn's disease and vice versa, i.e. both diseases also have a common genetic basis. Conversely, these findings mean that the environmental factors discussed above predominate in both conditions, but especially in ulcerative colitis. The genetic predisposition to inflammatory bowel disease is generally an extremely complex multigenetic process involving single nucleotide polymorphisms (SNPs) and polymorphisms of gene copy number, with 163 different relevant gene loci currently identified. The contribution of each individual locus to the risk is low; overall, only some of the genetic risk for this disease has been identified. Fifty of these genes have similar importance for Crohn's disease and ulcerative colitis, and 60 show heterogeneous effects. A further 30 are apparently specific to Crohn's disease and 23 specific to ulcerative colitis. The IBD genome is enriched 5-fold by associations that were previously described for immune defects; there are other associations with cytokine production, lymphocyte activation and antibacterial activity. Single gene defects with intestinal inflammation have also been identified, however, for example in the interleukin 10 (IL-10) receptor, in which affected individuals then develop the disease usually very early in childhood. In the context of genome-wide studies, not just the nature but also the site and course of diseases have recently been considered. Thus, Crohn's of the small intestine and Crohn's of the large intestine as well as ulcerative colitis are now described separately as a genetic continuum. This is also absolutely essential in view of the diversity of the phenotype described below.

The most important and best demonstrated association is between Crohn's disease and the intracellular receptor NOD2, which can bind muramyl dipeptide from the bacterial membrane and then trigger a protective signalling cascade. The risk of Crohn's disease increases by a factor of 2.4 if there are single nucleotide polymorphisms in NOD2 in a heterozygous manner and by as much as 17.1 in the case of a homozygous mutation. Nevertheless, most individuals with homozygous mutations do not develop any disease, i.e. there is no single gene association. Interestingly, the Crohn's-associated NOD2 mutations presumably lead to loss of function and thus not to an excessive reaction, as had actually been expected. Instead, they are associated with a defect in defensin expression in the terminal ileum (Paneth cells). This fits very well with the observation of a strong association with Crohn's of the ileum, while Crohn's disease of the colon is independent of NOD2.

The autophagy factor ATG16L1 is also associated primarily with Crohn's disease of the ileum. Autophagy is a mechanism for breaking down a cell's own structures but also those of bacteria. In animal studies, mice with a genetically induced defect of this protein show a major abnormality of the Paneth cell granules, with the exact mechanism still not being clear. A further factor in connection with the Paneth cell is XBP1, which plays a role in endosomal stress and probably also has Crohn's-associated mutations.

The Wnt system, which, as discussed below, plays a central role in Paneth cell differentiation, is probably also important. After reduced expression of the Wnt signalling pathway factor TCF4 was noted, a genetic association with Crohn's disease of the ileum, especially severe forms with stenosis, was identified with an odds ratio of 1.5. The Wnt receptor LRP6 is genetically associated with Crohn's disease, especially disease occurring early in childhood and adolescence. Other genetic associations have been found for various transporters (OCT1, OCT2, MDR1) and membrane proteins (DLG5).

There is much less data on Crohn's disease affecting the colon. This is probably because genetic