The role of intestinal bacterial flora in the pathogenesis of inflammatory bowel diseases. A two-component hypothesis

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Abstract. *According to the two-component hypothesis, the primary lesion of idiopathic proctocolitis (ulcerative colitis) consists of a hemorrhagico-catarrhal inflammation of unknown (idiopathic) aetiology appearing and disappearing periodically. The secondary component is an ulcerative inflammation caused by invasion of potential pathogenic intestinal microorganisms as well as disturbance of immunity, sensitisation and deficiencies etc. This component may be superimposed upon other primary lesions and suppresses or destroys their typical features so that advanced stages of ulcerative inflammations of any origin may have similar morphological features. This makes difficult their differential diagnosis, which must be based not solely on pathology but also on clinical features. This hypothesis helps to explain the effect of anti-infectious treatment which may be effective in the ulcerative stage but not in the hemorrhagico-catarrhal stage of ulcerative colitis. It helps us to understand the paradox that some severe forms are relatively better controlled by treatment than the mild cases, which are often resistant to therapy. In order to avoid ambiguity of the term ulcerative colitis, the term idiopathic proctocolitis has been proposed as a more precise term for both forms of the disease characterized in the mild rectal form by hemorrhagico-catarrhal inflammation and in the severe subtotal or total form by purulent and ulcerative process. This term has the advantages of being unequivocal and of stressing the two main characteristics of the disease entity.*

Key words: *inflammatory bowel disease, ulcerative colitis, idiopathic proctocolitis, intestinal microflora, pathogenesis of colitis, indeterminate colitis.*

Mařatka Z. Význam střevní bakteriální flóry v patogeneze idiopatických střevních zánětů. Dvousložková hypotéza patogeneze idiopatické proktokolitidy. Folia Gastroenterol Hepatol 2003; 1: 6 - 11.

Souhrn. *Podle této hypotézy, která se zakládá na bakteriologických a klinických studiích, primární poruchou je hemoragicko-katarální zánět neznámé (idiopatické) etiologie s periodickým průběhem. Sekundární složku tvoří hnisavě vředovitý zánět podmíněný potenciálně patogenními střevními mikroorganismy a dalšími mechanismy - poruchami imunity, senzibilizací, karencemi apod. Tato složka se připojuje i k primárním poruchám jiného původu a překrývá jejich typické známky, takže vředovité záněty tlustého střeva mají mnoho morfologických podobností. To znesnadňuje jejich diferenciální diagnózu, která se proto nemůže zakládat jen na histopatologii, nýbrž musí přihlížet i ke klinické symptoma-*

tologii. Dvousložková hypotéza přispívá k vysvětlení účinků antiinfekčních léků, které mohou působit kausálně na sekundární vředovitý zánět, ale nemají vliv na složku základní. Tím se vysvětluje paradox, že těžké formy nemoci jsou poměrně lépe přístupné léčbě než formy lehké, u nichž je dosud známa jen symptomatická terapie proti mechanismu zánětu. Aby se zamezilo dvojsmyslnosti termínu ulcerózní kolitida, navrhujeme pro nemoc, která má v lehké formě ráz katarálně hemoragický a v těžké formě ráz vředovitý, název idiopatická proktokolitida, což vystihuje obě hlavní charakteristiky této chorobné jednotky.

Klíčová slova: *idiopatické střevní záněty, ulcerózní kolitida, idiopatická proktokolitida, střevní mikroflóra, patogeneze kolitidy, indeterminovaná kolitida.*

The aetiology of inflammatory bowel diseases (IBD) - idiopathic proctocolitis (ulcerative colitis, UC) and Crohn's disease (CD) is not yet elucidated but their pathogenesis, i.e. the sequence of events by which the disease develops is partly known. Recently the role of kinins, eicosanoids and various immunological agents in the development of intestinal inflammation has been intensively studied and their significance documented. This aspect has overshadowed the importance of *infection*, which was the main subject of research in the past. In this article the role of infection will be discussed, however, attention will not be directed towards external pathogens but towards the microorganisms, which are common inhabitants of the intestine.

The large intestine differs from other digestive organs by being infested with millions of microorganisms, which under normal conditions perform their useful physiological functions as innocuous commensals but in cases of altered milieu or decreased resistance, acquire pathogenicity and behave as pathogens (4,7,28). The participation of intestinal flora in the pathogenesis of IBD has been subject to our experimental and clinical studies, which will be summarized in this article.

EXPERIMENTAL STUDIES

Bacteriological, serological and immunological studies performed in collaboration with Wagner have been revised and re-evaluated (31). Stool and rectal smears from 31 ulcerative colitis patients were examined. Bacteriological examinations revealed various potentionally pathogenic commensals, especially Escherichia coli in 80%, paracoli (i.e. other Enterobacteriaceae) in 33%, alfa/gama streptococci in 33%, other bacteria more rarely but none of them were associated with this disease permanently or uniquely. The majority of them elicited definite allergic and immunologic reactions proved by positive agglutination and skin tests. This was considered to be evidence of their pathogenity. Treatment by autogenous vaccine prepared from the pathogenic bacteria was performed and evaluated in a follow-up of several years in 35 patients with ulcerative colitis. This treatment was found to be a valuable supportive measure due to the effect on secondary infection and sensitation (24). The role of immunity and autoimmunity in the pathogenesis of ulcerative colitis was assessed by evidence of circulating anti-colon antibodies and autoantibodies (25,32). In spite of some positive findings, neither diagnostic nor prognostic value of this method could be proved (26).

Discussion

The results of the above-mentioned bacteriological-serological studies are in keeping with the data from the literature pointing to the importance of the intestinal microorganisms, which under normal circumstances are innocuous commensals whilst in abnormal conditions acquire pathogenity and participate in the development of morphological changes and clinical symptomatology.

An impulse for the change from innocuous saprophytes and commensals to pathogens may arise from various non-specific causes - change of intestinal environment due to transient infection, offensive food, loss of resistance due to trauma, ischaemia, vascular disorder, nutritional or vitamin deficit as well as neurogenic or psychogenic disturbances etc. Haemolytic streptococci were increased in ulcerative colitis probably due

to the presence of blood in the faeces (1). Haemolytic and necrotoxic strains of Escherichia coli with adhesive and invasive character were found in the intestinal contents (3) as a consequence of an altered milieu (2).

The pathogenic effect of the intestinal microflora was shown to be due to the process of *translocation*, i.e. penetration of bacteria through the intestinal barrier (10). In this case, antigens and bacteria pervade the barrier of the intestinal mucosa, immune complexes enter the circulation and immunological abnormalities of all kinds develop. This has been shown in many conditions including postoperative sepsis, pancreatitis, liver cirrhosis, intestinal obstruction as well as in IBD - not only in ulcerative colitis (7) but also in diversion colitis (6) and after by-pass operations for obesity (30). Recently the pathogenic role of colonic flora was shown in Crohn's disease by establishing mutations of the susceptibility gene NOD2 (CARD15), which governs the defence of the intestine against colonic bacteria (5,9).

It can be concluded that the experimental evidence has confirmed that intestinal microorganisms participate in the pathogenesis of ulcerative colitis and other intestinal inflammations. Their actual role in the symptomatology and evolution of the disease has been subject to clinical studies.

CLINICAL STUDIES

These studies were based on 1,262 cases of IBD: 959 idiopathic proctocolitis (ulcerative colitis) (22) and 303 Crohn's disease (8). In 19 cases, a definite diagnosis could not be established (1.4%). The cases were revised and analysed with particular reference to the clinical course, symptomatology and response to the treatment in different stages of the disease. Conditions for this type of study were suitable because of the length of the disease and follow-up (up to 40 years) as well as the fact that it was performed from 1942 until 1984 at a time when at least in the first two decades, no potent drugs were available and the natural history of the disease was not biased by the therapy. A graphical method was used to illustrate the course of the disease. The results can be summarized as follows (11,23):

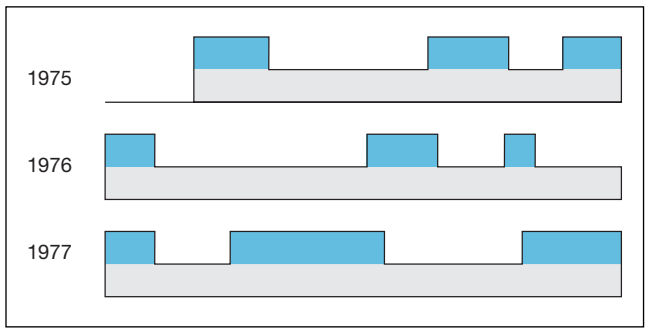

Fig. 1. **Remittent type of UC. Frequent symptomatic relapses, short remissions with lasting morphological abnormalities.**

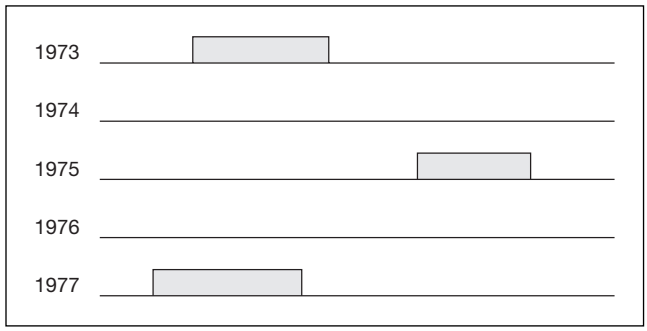

Fig. 2. **Intermittent type of UC. Rare recurrences, long asymptomatic intervals with (almost) complete morphological recovery.**

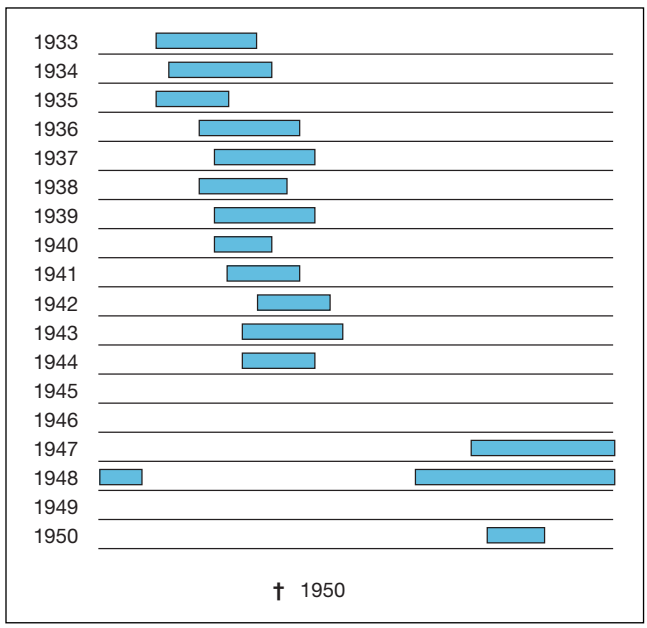

Fig. 3. **Seasonal type of UC. Regularly relapsing recurrences.**

Three basic types of the course of UC were established: 1. *Remittent type* (Fig. 1) with frequent symptomatic relapses and short remissions with lasting residual morphological changes; 2. *Intermittent type* (Fig. 2) with rare recurrences and long asymptomatic intervals; 3. *Seasonal type* (Fig. 3) with regularly relapsing attacks.

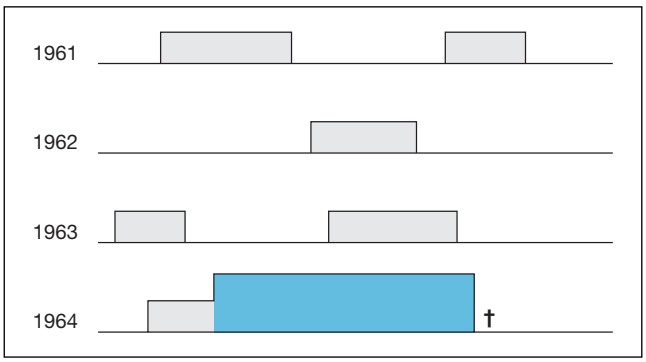

Fig. 4. **Change from mild distal colitis to severe pancolitis. After several mild attacks, the disease progressed to a severe form and death.**

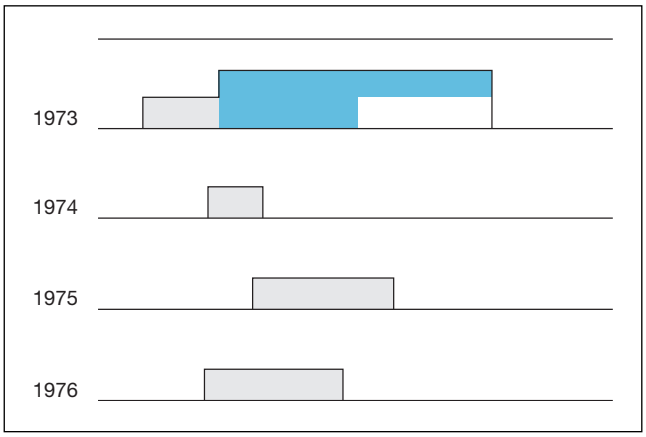

Fig. 5. **Change from severe disease to mild form. After the patient survived a severe attack of UC, the disease continued with seasonal periodicity of mild recurrences.**

Those were cases of a *mild form*, presented as a catarrhal-hemorrhagic inflammation of the terminal part of the colon. Conversely *the severe form* was presented as an ulcerative inflammation with subtotal or total involvement of the rectum and colon with symptoms of toxicosis and sepsis (Figs. 4, 5). Whereas mild cases were resistant to the anti-infectious treatment, the symptoms in some severe cases could be partly or fully controlled by antibiotics. Noteworthy were cases with seasonal type in which the mild form switched to a severe form outlasting the usual duration of the attack. In some of such cases, antibiotic treatment brought about quick recovery and this was explained as being due to the fact that the primary process was in remission at that time and the ulcerative process was a result of outlasting infection (Fig. 6). This interpretation was supported by the results of colectomy with ileorectal anastomosis, which was the operation of preference at that time. Proctitis continued in

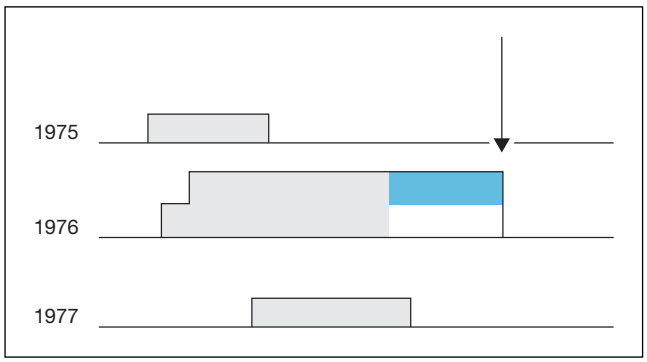

Fig. 6. **The effect of antibiotics concerning severe pancolitis. On second attack, the disease progressed to severe pancolitis outlasting the duration of seasonal activity. Antibiotic therapy at this time (arrow) resulted in quick recovery.**

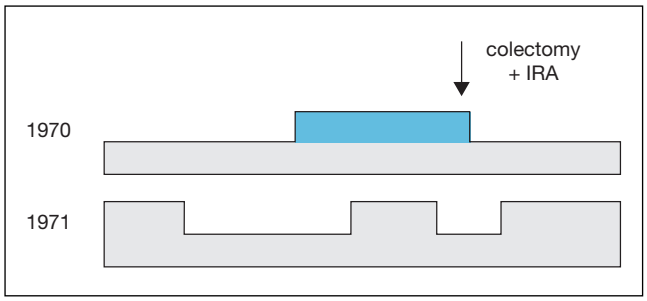

Fig. 7. **Colectomy with ileorectal anastomosis with partial effect. Proctitis continued in the rectal stump when the operation was performed in the UC stage of activity.**

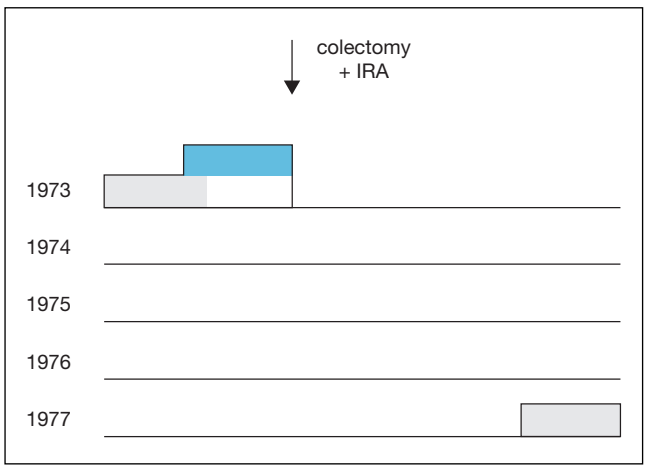

Fig. 8. **Colectomy with ileorectal anastomosis with excellent effect. Proctitis disappeared in the rectal stump when the operation was performed in the UC stage of inactivity.**

the rectal stump in some cases in which the operation was probably performed in the period of UC activity (Fig. 7). Conversely active proctitis in the stump disappeared when the operation was performed in the period of inactivity and recurred only in the distant future (Fig. 8). Such experience was the starting point for the concept of the ***two-component hypothesis***.

THE TWO-COMPONENT HYPOTHESIS OF ULCERATIVE COLITIS

The non-specific character of the secondary ulcerative changes is the reason why purely morphological findings at the time of the examination often are not sufficient to establish a clinical diagnosis. A clue to the diagnosis may yield the evolution of the disease, i.e. its course, periodicity, way of extension, distribution of lesions and complications.

This was the idea of a working hypothesis of the pathogenesis of idiopathic proctocolitis leading to the concept of the *two-component hypothesis*. This hypothesis was put forward in 1948 (12). Since then, more evidence has been assembled from research (15,17,18) and from literature and a final version was published in 1993 (16). This hypothesis was proposed for *idiopathic proctocolitis (ulcerative colitis)* but it may be valid for other inflammatory diseases of the colon as well. According to it, lesions in the large intestine of a different nature are exposed to and secondarily infected by the intestinal flora, which under abnormal conditions acquires pathogenity. As a result, suppuration and ulceration is superimposed on the primary lesion and the ensuing ulcerative inflammation overshadows its features. The primary component is responsible for the mild form, the secondary component for the severe form of UC.

The two-component hypothesis offers interesting ideas and helps us to understand some problematic or controversial issues which will be mentioned in the following paragraphs.

Ambiguity of the term "ulcerative colitis"

The ulcerative inflammation caused by pathogenic intestinal flora is a non-specific process caused by various microorganisms and engrafted on different primary lesions. It is a true "ulcerative colitis" in the descriptive morphological sense. Irrespective of the eliciting cause, such ulcerative inflammation has similar macro- and microscopic appearances and because of extensive destruction of tissue, suppresses or eliminates the traits characteristic of the original lesion. In order to avoid misunderstanding, which may arise as a result of the ambiguity of the term "ulcerative colitis", the term idiopathic proctocolitis has been proposed for the clinical entity characterized by hemorrhagic-catarrhal inflammation in the mild distal form and by ulcerative inflammation in the severe (sub)total form (14). This term has the advantage that it aptly and unequivocally identifies the disease entity and states its main characteristics, namely the idiopathic nature (constitutional character, unknown aetiology) and involvement of the rectum and adjacent colon. A similar term has been used in the French medicine (rectocolite hemorrhagico-ulcéreuse).

Role of histopathology

Histopathology of idiopathic proctocolitis may be flawed by the fact that advanced stages reflect the non-specific changes of the secondary ulcerative inflammation, which may overshadow the morphological character of the basic lesion. This is the reason why advanced stages of intestinal inflammations have similar appearances, making their differential diagnosis difficult (13,20,21). Specific features of diseases of the colon should be looked for in the early stages when the typical characteristics are not destroyed by secondary infection.

"INDETERMINATE COLITIS" (27,29,33)

This term has been used by some authors for cases in which they feel unable to establish a definite diagnosis of the type of IBD. According to the two-component hypothesis, this term should not represent another disease entity but a non-specific ulcerative inflammation engrafted on primary diseases of various origin (19). The term is not well chosen because the condition is not *indeterminate* but *non-determined* (ulcerative inflammation of unidentified origin).

BACTERIAL TRANSLOCATION IN CROHN'S DISEASE AND IN OTHER INTESTINAL INFLAMMATIONS

The phenomenon of secondary infection by pathogenic intestinal flora may also be relevant to other intestinal diseases, especially to Crohn's disease. In contrast to idiopathic proctocolitis, there is a difference in its occurrence. In the rectal form of idiopathic proctocolitis, the translocation of bacteria does not occur. Syste-

mic response with laboratory abnormalities appears in severe, more extensive forms when the intestinal barrier is disturbed. In Crohn's disease the lesion affects the deeper layers of the intestinal wall and the intestinal barrier is disturbed from the beginning. This is why systemic response and biochemical abnormalities occur in the active disease irrespective of location and extent. The pathogenic potential of intestinal microflora, of course, may be pertinent to any condition disturbing the integrity of the intestinal barrier.

THERAPY

From the standpoint of the two-component hypothesis, two groups of drugs can be distinguished in the present therapy of IBD: 1. Anti-inflammatory drugs (aminosalicylates, corticosteroids) affecting the mechanisms on inflammation of the primary component - not its aetiology (hence symptomatic); 2. Anti-infectious drugs (antibiotics etc.) affecting the infection of the second component (possibly causal). The role of probiotics in controlling the intestinal microflora has recently been given attention with some promising results.

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