The hygiene hypothesis and inflammatory bowel diseases : role of helminths

Tom G. Moreels, Paul A. Pelckmans

University Hospital Antwerp, Division of Gastroenterology & Hepatology

Abstract

The incidence of atopic and immune diseases has dramatically increased during the second half of the twentieth century. This has been attributed to improved sanitation and hygiene with reduced exposure to infections. The concept of this *hygiene hypothesis* is not new, and is currently used to explain the increasing incidence of a wide area of diseases. Parasitic helminths are powerful modulators of their host's immune system. It is suggested that the reduced exposure to helminths, due to better hygiene conditions, may predispose to the development of inflammatory bowel diseases. This article reviews the current epidemiological, experimental and clinical data supporting the role of helminths in the hygiene hypothesis in inflammatory bowel diseases. (Acta gastroenterol. belg., **2006**, 69, **413-417**).

Key words : Crohn's disease, helminths, hygiene hypothesis, inflammatory bowel disease, review, ulcerative colitis.

Introduction

Inflammatory bowel disease (IBD) is a chronic relapsing condition of the gastrointestinal tract that manifests as Crohn's disease, ulcerative colitis or indeterminate colitis (1). Although clinical descriptions of chronic inflammatory bowel diseases go back to the 17th century, the aetiology still remains unknown (2). It is thought to result from inappropriate and ongoing activation of the mucosal immune system driven by the presence of normal gut flora (1). In addition, epidemiological and laboratory work suggests that environmental and genetic factors play an important role in the pathogenesis of IBD (3). Smoking increases the risk of Crohn's disease, whereas it has a protective effect on the development of ulcerative colitis, as does appendectomy at a young age (4,5). Also, genetic factors are important in the pathogenesis of both Crohn's disease and ulcerative colitis (6). However, these factors cannot explain why the incidence of IBD has dramatically increased over the last five decades, especially in the developed world (7,8).

The hygiene hypothesis

The reason for this increase in incidence of IBD may be explained by the hygiene hypothesis. It states that raising children in extremely hygienic conditions is a predisposition to develop immune diseases like IBD (8,9). The decreased exposure to viral, bacterial and helminth infections, due to better hygiene, sanitation and medical conditions, may negatively affect the development of the immune system, rendering it more prone for immune diseases. However, the hygiene hypothesis is not a new concept. Already in 1963 it was hypothesised that development of the neuro-immune disease multiple sclerosis is correlated with high level of sanitation in childhood (10). Later on in 1966 a large scale epidemiological study confirmed the relationship between high sanitation levels in childhood and development of multiple sclerosis in adulthood (11). A population-based study in 1976 revealed a relationship between the decreased exposure to infections and the development of atopic diseases like asthma, eczema and urticaria (12). This study concluded that "*atopic disease is the price paid by some members of the white community for their relative freedom from diseases due to viruses, bacteria and helminths*". In 1989 Strachan named this phenomenon the hygiene hypothesis (13).

Since then, the hygiene hypothesis is postulated to play a role in the increased incidence of several atopic and (auto-) immune diseases (14). A first group consists of atopic diseases like asthma, dermatitis, urticaria, hay fever and allergic rhinoconjunctivitis (15). Based on epidemiological studies type 1 diabetes mellitus (16), multiple sclerosis (11), Graves' hyperthyroidism (17), glomerulonephritis (18), arteriosclerosis and heart disease (19), irritable bowel syndrome (20) and IBD (21) are also associated with the hygiene hypothesis.

Several epidemiological observations illustrate the link between the hygiene hypothesis and IBD. The incidence of IBD is highest in the developed world (22), and is reported only sporadically in the developing countries of middle Africa (23,24) and South America (25), where helminth infections are widespread (26). In countries with low infant mortality, a reflection of better hygiene and medical conditions, the incidence of IBD is higher than in countries with low hygiene standards and high infant mortality (27). This is also shown by better sanitation conditions, based on the presence of hot water taps and separate bathrooms, during early childhood in patients with Crohn's disease (28). In general, there is a positive correlation between the incidence of IBD and the socioeconomic status (29).

Corresponding author : Tom G. Moreels, University Hospital Antwerp, Division of Gastroenterology & Hepatology, Wilrijkstraat 10, B-2650 Antwerp, Belgium. E-mail : tom.moreels@uza.be.

Submission date :
Acceptance date :

Immunology of the gastrointestinal mucosa

Local defence mechanisms in the gastrointestinal tract

The pathogenic background of the hygiene hypothesis in IBD is based on specific features of the immune system, especially in the gut-associated lymphoid tissue or GALT (9). One major function of the intestinal immune system is to maintain immunoregulatory mechanisms that down-regulate responses to ubiquitous antigens from food and bacterial flora, while retaining the ability to respond to pathogens. Saliva and mucus production, gastric and pancreatic juice, gastrointestinal propulsive motility, and epithelial cell proliferation and migration are all mechanisms acting to avoid pathogens to attach and break through the epithelial barrier. Once this first line of defence is trespassed, the pathogen encounters the innate and acquired immune system within the intestinal mucosa. Both systems work in close interaction to eliminate pathogens (30,31).

The innate immune responses use a wide variety of cells leading to phagocytosis (dendritic cells and macrophages), release of inflammatory mediators (polymorphonuclear leucocytes and mastcells) and natural killer cells. Innate immune responses occur to the same extent however many times the pathogen is encountered. On the other hand, acquired immune responses are pathogen-specific and improve on repeated exposure to a given pathogen. They imply the proliferation of antigen-specific B and T lymphocytes. These lymphocytes are activated upon direct contact with pathogen-derived antigen, expressed on the surface of antigen-presenting cells like dendritic cells and macrophages. Activated B lymphocytes secrete immunoglobulins which are antigen-specific antibodies that bind and eliminate extracellular pathogens. T lymphocytes eradicate intracellular pathogens, and mediate antihelminth and allergic responses. Different subtypes of T lymphocytes are distinguished on the basis of cell-surface CD-antigens and on the basis of released cytokines. T helper (Th) cells carry $CD4^+$ antigens on their surface. $CD8^+$ cells are cytotoxic T cells and regulatory T (Treg) cells are $CD25^+$, which are also characterised by the release of the anti-inflammatory cytokines interleukin (IL) 10 and tissue growth factor (TGF) β. Based on their cytokine release upon activation by an antigen-presenting cell, Th cells are further subdivided into Th1 and Th2 cells. Th1 cells are engaged in cell-mediated immunity against bacteria and viruses, and are characterised by the secretion of interferon (IFN) γ and IL2. Th2 cells regulate antibody production and immune responses against helminths and allergens by the secretion of IL4, IL5 and IL13.

Regulation of the gastrointestinal immune system

Particular gastrointestinal diseases are associated with either Th1 or Th2 polarisation of the immune system. The inflammatory process in Crohn's disease and *Helicobacter pylori* gastritis is Th1 mediated (32,33), whereas helminthic infections induce a Th2 immune response (34). Ulcerative colitis shows both Th1 and Th2 features, depending on the activity and the location of the disease (35,36). The Th1/Th2 balance is not only regulated by the type of pathogen, but also by the local cytokine environment within the intestinal mucosa. The presence of IL12 stimulates the differentiation and proliferation of Th1 lymphocytes whereas IL4 tips the balance in favour of Th2 lymphocytes. Furthermore, there is a reciprocal down-regulation of Th1 proliferation by Th2 cytokines and *vice versa*. Finally, Treg lymphocytes, formally designated as suppressor T cells, suppress the differentiation of both Th1 and Th2 lymphocytes by the secretion of IL10 and TGFβ. Helminths are strong inducers of Treg cell proliferation, leading to a more immunosuppressive state helping them to survive by escaping the host's immune response.

The cross-inhibitory Th1/Th2 balance and the immunosuppressive function of Treg lymphocytes are important regulatory mechanisms of the gastrointestinal immune system. Defects of these regulatory mechanisms may lead to development of specific Th1- or Th2-mediated diseases. This forms the pathogenic basis of the hygiene hypothesis in IBD. The decreased exposure to helminth infections in the developed world leads to an underdevelopment of Th2 and Treg cell clones, rendering the intestinal immune system more prone to Th1-mediated diseases like Crohn's disease. However, the incidences of atopic diseases like asthma and eczema, which are marked Th2-mediated diseases, and ulcerative colitis, with both Th1 and Th2 characteristics, are also increasing in the developed world (14). Therefore, the role of Treg cells is probably more important than the Th1/Th2 balance in the hygiene hypothesis. They are considered real gatekeepers of the mucosal immune system (37). Moreover, IBD is associated with defective Treg cell activation, highlighting the importance of Treg cells in the control of mucosal inflammation (38). These mucosal regulatory mechanisms may be of benefit in the prevention or treatment of diseases with specific Th1 or Th2 features (39). For example, the Th2 polarisation and Treg cell proliferation induced by helminth infections can inhibit the Th1-mediated inflammatory process in IBD.

Experimental data supporting the hygiene hypothesis

A vast amount of experimental data now supports the role of helminths in the hygiene hypothesis for IBD. The possible beneficial effects of helminth infections on the development and the course of IBD have been investigated in different animal models. Even before the hygiene hypothesis was proposed in the aetiology of IBD, several studies had already provided data supporting it. In 1992 it was shown that infection of mice with the trematode *Schistosoma mansoni* reduced the

Table 1. — **Experimental animal studies with beneficial effects of helminths on colitis**

Author	Year	Helminth	Class	Host	Colitis	Effect	Reference
Reardon	2001	*Hymenolepsis diminuta*	cestode	mouse	DSS	prevent + cure	42
Kahn	2002	*Trichinella spiralis*	nematode	mouse	DNBS	prevent	44
Elliott	2003	*Schistosoma mansoni*	trematode	mouse	TNBS	prevent	45
Moreels	2004	*Schistosoma mansoni*	trematode	rat	TNBS	prevent	46
Elliott	2004	*Heligmosomoides polygyrus*	nematode	mouse	piroxicam + IL10$^{-/-}$	prevent	47
Hunter	2005	*Hymenolepsis diminuta*	cestode	mouse + rat	DNBS	prevent + cure	43

DSS : dextran sulfate sodium
DNBS : dinitrobenzene sulfonic acid
TNBS : trinitrobenzene sulfonic acid
IL10$^{-/-}$: interleukin 10-deficient.

production of Th1 cytokines in isolated spleen cells in response to a non-parasite antigen, illustrating the potential beneficial effects of helminths in specific Th1-mediated diseases (40). In 1997, overexpression of IL4, one of the major Th2 cytokines, reduced the duration of Th1-mediated inflammation in a rat model of trinitrobenzene sulfonic acid (TNBS)-induced colitis (41).

Instead of focussing on one single cytokine to counteract intestinal inflammation, Elliott *et al*. suggested the use of helminths, as inducers of Th2 and Treg cells and their respective cytokines, opening the door for the hygiene hypothesis to IBD (21). With this approach, a combination of Th2- and Treg-derived immune modulatory cytokines may exert overt anti-inflammatory actions in Th1-mediated models inflammation. Moreover, this experimental set-up mimics the situation in the developing world, where helminth infections are endemic. The first complete report on the beneficial effect of helminths on the course of Th1-mediated experimental colitis was published in 2001. Reardon *et al*. were able to show that infection of mice with the cestode *Hymenolepsis diminuta* both prevented and inhibited mucosal hypersecretion in dextran sulfate sodium (DSS)-induced colitis (42). Since then, several studies showed that helminth infections of different species have beneficial preventive and therapeutic effects on experimental Th1-mediated colitis (Table 1). The same group elaborated further on the prophylactic and therapeutic effect of *H. diminuta* infection in dinitrobenzene sulfonic acid (DNBS)-induced colitis in both mice and rats (43). Also, prior infection of mice with the nematode *Trichinella spiralis* reduced the severity of DNBS-induced colitis (44). Intraperitoneal injection of inactivated eggs of the trematode *Schistosoma mansoni* prevents TNBS-induced colitis in mice (45) and transcutaneous infection of the semipermissive rat host with *S. mansoni* also attenuates TNBS-induced colitis (46). Finally, colonization of piroxicam-treated colitic IL10-deficient mice with the nematode *Heligmosomoides polygyrus* suppressed established inflammation through a Treg cell-dependent mechanism (47). These studies clearly indicate that several types of helminths exert both prophylactic and therapeutic efficiency in different models of experimental colitis in rodents.

Clinical data supporting the hygiene hypothesis

The beneficial actions of helminths in gastrointestinal inflammation are not only limited to experimental animal studies. Based on their promising results in a mouse model of colitis, the group of Weinstock *et al*. started clinical studies with the pig whipworm *Trichuris suis* in patients with IBD refractory to conventional therapy. *T. suis* is not a human parasite, and therefore not expected to be invasive or to cause disease (48). The embryonated eggs hatch and release first stage larvae into the proximal small bowel, where they mature and then move down the intestinal lumen to the caecum. Within the colon, only the head of the parasite attaches to the mucosal epithelium without causing any damage or entering the systemic circulation. After a few weeks, the parasite is spontaneously expelled with the stools from the colon without the risk of colonizing other human hosts, because it needs an incubation period of about two weeks in the soil, which is precluded by current sanitation standards.

The authors presented their preliminary results on three patients with refractory Crohn's disease at the *Digestive Disease Week* in San Diego in 1999 (49). A dose of 2500 live embryonated eggs were given orally without change in baseline IBD medications. A substantial clinical improvement in all three patients was reported as reflected by a drop of the Crohn's disease activity index (CDAI) and improvement of the IBD quality-of-life index (IBDQ). Since then the number of patients with refractory Crohn's disease treated with *T. suis* ova has increased. Recently, an open label study of 29 patients was published and reported a beneficial effect of three weekly repeated oral administration of 2500 infective eggs of *T. suis* (50). Clinical response was defined as a decrease in CDAI of more than 100 points and clinical remission was defined as CDAI below 150. After 12 weeks 75.9% of the patients responded with 65.5% reaching remission. After 24 weeks these numbers were 79.3% and 72.4% respectively. Patients were kept on their standard IBD medications throughout the course of the study. Subset analysis of patient characteristics suggested that the current use of immunosuppressive drugs and the absence of ileocecal resection may aid

the beneficial effect of *T. suis* therapy. Although the study is an open trial, the high response rate cannot be explained solely on the basis of a significant placebo effect. These promising results must be confirmed by a double blind, placebo-controlled trial.

The same authors conducted a double blind, placebo-controlled trial in 54 patients with active ulcerative colitis (51). All patients had moderately active ulcerative colitis defined by the Ulcerative Colitis Disease Activity Index (UCDAI) score ≥ 4. Twenty-four patients received placebo and 30 patients were treated with oral administration of 2500 infective eggs of *T. suis* every two weeks for 12 weeks. Clinical response was defined as a decrease in UCDAI of at least 4 points and clinical remission was defined as UCDAI of maximum 2 points. After 12 weeks clinical response was obtained in a significantly higher number of patients (43.4%) treated with *T. suis* as compared to the placebo group (16.7%). No statistically significant difference was found in the respective numbers of clinical remission (10% in *T. suis* group *versus* 4% in placebo group).

These two clinical trials for the treatment of IBD with live *T. suis* eggs have an important innovative impact, opening the door to a new area of therapeutic options. Although the reported numbers of treated patients are small, the overall result appears to be beneficial and safe. So far, no adverse effects of *T. suis* therapy were encountered. It is expected that the studies will be continued to increase the number of patients. The higher response rate in Crohn's disease may in part be explained by a higher placebo effect, which is expected in open trials as compared to double blind, placebo-controlled trials. Additionally, the differences in the underlying immunologic characteristics of Crohn's disease and ulcerative colitis may provide another explanation. Crohn's disease has specific Th1 characteristics, whereas the inflammatory process in ulcerative colitis shows both Th1 and Th2 features. Therefore, one may postulate that patients with Crohn's disease benefit more of treatment with *T. suis* since helminths suppress Th1-mediated inflammation through both Th2- and Treg-mediated mechanisms.

Future perspectives

The potential beneficial effects of helminths are currently under clinical investigation in a wide area of atopic and immune diseases. The promising studies with the pig whipworm *T. suis* in IBD have been discussed above. A large international multi-centre trial is in preparation. Also a study on the effect of controlled hookworm (*Necator americanus*) infection on allergic asthma will soon be initiated (52). The increasing interest in helminths as immune modulators led to the first international *Workshop on Helminths as Modulators of Immunity*, which was held in Hamburg in June 2005. However, many questions remain unanswered at this moment. Will helminth-based therapy prove beneficial in large multi-centre trials ? Is it a life-long therapy ? Is it safe ? Can it be used to prevent the development of IBD ?

The clinical use of viable eggs of helminths for the treatment of atopic or immune diseases evokes some safety concerns (53,54). In addition, patients may be reluctant to ingest worm eggs or to the idea of developing intestinal parasites, even only temporarily. Therefore, it is important to continue the research on helminth-based therapies. One step further in this search would be the identification, isolation and production of specific helminth antigens with immune modulatory activities (55). Helminths can express 20,000 genes, but not all gene products interact with the host's immune system. It is hypothesised that a combination of antigens, containing both proteoglycans and lipopolysaccharides from both eggs and adult worms, may have the same beneficial effects on the course of atopic and immune diseases as compared to the currently used viable embryonated worm eggs. This will certainly have many advantages. First of all, the safety issue on possible invasion of parasites into the systemic circulation is avoided. Individual molecules can be bio-engineered which allows large scale production and use. Although their mode of application to patients is not yet established, they will be regarded as 'medication' instead of worm eggs.

Conclusions

Although the hygiene hypothesis is not a new concept, it has recently regained a lot of attention with the beneficial results of the clinical *T. suis* trials in IBD. The increased standards of sanitation and health care have led to decreased exposure to infections in general and helminth infections in particular, leading to changes in the immune system and rendering patients more prone to the development of atopic and immune diseases. The hygiene hypothesis is now supported by a vast amount of both epidemiologic, animal and human studies, making it more a hygiene theory than hypothesis. It is opening the door to a new era of therapeutic evolutions, of which we have so far only witnessed the promising beginning.

References

1. PODOLSKY D.K. Inflammatory bowel disease. *N. Eng. J. Med*., 2002, **347** : 417-429.
2. KIRSNER J.B. Historical origins of current IBD concepts. *World J. Gastroenterol*., 2001, **7** : 175-184.
3. FIOCCHI C. Inflammatory bowel disease : etiology and pathogenesis. *Gastroenterology*, 1998, **115** : 182-205.
4. CALKINS B.M. A meta-analysis of the role of smoking in inflammatory bowel disease. *Dig. Dis. Sci.*, 1989, **34** : 1841-1854.
5. KOUTROUBAKIS I.E., VLACHONIKOLIS I.G. Appendectomy and the development of ulcerative colitis : results of a meta-analysis of published case-control studies. *Am. J. Gastroenterol*., 2000, **95** : 171-176.
6. BONEN D.K., CHO J.H. The genetics of inflammatory bowel disease. *Gastroenterology*, 2003, **124** : 521-536.

7. LAPIDUS A. The changing epidemiology of inflammatory bowel disease. *Acta Gastroenterol. Belg*., 2001, 64 : 155-159.
8. ELLIOTT D.E., SUMMER R.W., WEINSTOCK J.V. Helminths and the modulation of mucosal inflammation. *Curr. Opin. Gastroenterol*., 2004, **21** : 51-58.
9. MOREELS T.G., PELCKMANS P.A. Gastrointestinal parasites. Potential therapy for refractory inflammatory bowel diseases. *Inflamm. Bowel Dis*., 2005, **11** : 178-184.
10. POSKANZER D.C., SCHAPIRA K., MILLER H. Multiple sclerosis and poliomyelitis. *Lancet*, 1963, **2** : 917-921.
11. LEIBOWITZ U., ANTONOVSKY A., MEDALIE J.M., SMITH H.A., HALPERN L., ALTER M. Epidemiological study of multiple sclerosis in Israel. II. Multiple sclerosis and level of sanitation. *J. Neurol. Neurosurg. Psychiatr.*, 1966, **29** : 60-68.
12. GERRARD J.W., GEDDES C.A., REGGIN P.L., GERRARD C.D., HORNE S. Serum IgE levels in white and metis communities in Saskatchewan. *Ann. Allergy*, 1976, **37** : 91-100.
13. STRACHAN D.P. Hay fever, hygiene, and household size. *Brit. Med J*., 1989, **299** : 1259-1260.
14. BACH J.F. The effect of infections on susceptibility to autoimmune and allergic diseases. *N. Engl. J. Med.*, 2002, **347** : 911-920.
15. YAZDANBAKHSH M., KREMSNER P.G., VAN REE R. Allergy, parasites, and the hygiene hypothesis. *Science*, 2002, **296** : 490-494.
16. GALE E.A.M. A missing link in the hygiene hypothesis ? *Diabetologia*, 2002, **45** : 588-594.
17. MC LACHLAN S.M. Graves'disease : the T_H1/T_H2 paradigm versus the "hygiene" hypothesis and defective immune regulation. *Thyroid*, 2003, **13** : 127-128.
18. HURTADO A., JOHNSON R.J. Hygiene hypothesis and prevalence of glomerulonephritis. *Kidney Int. Suppl.*, 2005, **97** : S62-S76.
19. MAGEN E., BORKOW G., BENTWICH Z., MISHAL J., SCHARF S. Can worms defend our hearts ? Chronic helminthic infections may attenuate the development of cardiovascular diseases. *Med. Hypoth.*, 2005, **64** : 904-909.
20. GWEE K.A. Irritable bowel syndrome in developing countries – a disorder of civilization or colonization ? *Neurogastroenterol. Mot.*, 2005, **17** : 317-324.
21. ELLIOTT D.E., URBAN J.F. Jr., ARGO C.K., WEINSTOCK J.V. Does the failure to acquire helminthic parasites predispose to Crohn's disease ? *FASEB J*., 2000, **14** : 1848-1855.
22. CALKINS B.M., MENDELOFF A.I. Epidemiology of inflammatory bowel disease. *Epidemiol. Rev.*, 1986, 8 : 60-91.
23. HUTT M.S.R. Epidemiology of chronic intestinal disease in Middle Africa. *Isr. J. Med. Sci*., 1979, **15** : 314-317.
24. MAYBERRY J., MANN R. Inflammatory bowel disease in rural Sub-Saharan Africa : rarity of diagnosis in patients attending mission hospitals. *Digestion*, 1989, **44** : 172-176.
25. ROLON P.A. Gastrointestinal pathology in South America. *Isr. J. Med. Sci.*, 1979, **15** : 318-321.
26. WORLD HEALTH ORGANIZATION. Major parasitic infections : a global review. *World Health Stat. Q*., 1986, **39** : 145-160.
27. MONTGOMERY S.C., POUNDER R.E., WAKEFIELD A.J. Infant mortality and the incidence of inflammatory bowel disease. *Lancet*, 1997, **349** : 472-473.
28. GENT A.E., HELLER M.D., GRACE R.H., SWARBRICK E.T., COGGON D. Inflammatory bowel disease and domestic hygiene in infancy. *Lancet*, 1994, **343** : 766-767.
29. ALIC M. Inflammatory bowel diseases are diseases of higher socioeconomic status : dogma or reality ? *Am. J. Gastroenterol*., 2000, **95** : 3332-3333.
30. DELVES P.J., ROITT I.M. The immune system. First of two parts. *N. Engl. J. Med*., 2000, **343** : 37-49.
31. DELVES P.J., ROITT I.M. The immune system. Second of two parts. *N. Engl. J. Med*., 2000, **343** : 108-117.
32. MAC DONALD T.T., MONTELEONE G., PENDER S.L.F. Recent development in the immunology of inflammatory bowel disease. *Scand. J. Immunol*., 2000, **51** : 2-9.
33. BAMFORD K.B., FAN X., CROWE S.E., LEARY J.F., GOURLEY W.K., LUTHRA G.K., BROOKS E.G., GRAHAM D.Y., REYES V.E., ERNST P.B. Lymphocytes in the human gastric mucosa during *Helicobacter pylori* have a T helper cell 1 phenotype. *Gastroenterology*, 1998, **114** : 482-492.
34. MAC DONALD A.S., ARAUJO M.I., PEARCE E.J. Immunology of parasitic helminth infections. *Infect. Immun*., 2002, **70** : 427-433.
35. INOUE S., MATSUMOTO T., IIDA M., MIZUNO M., KUROKI F., HOSHIKA K., SHIMIZU M. Characterization of cytokine expression in the rectal mucosa of ulcerative colitis : correlation with disease activity. *Am. J. Gastroenterol*., 1999, **94** : 2441-2446.
36. MATSUZAKI K., HOKARI R, KATO S., TSUZUKI Y., TANAKA H.F., KURIHARA C., IWAI A, KAWAGUCHI A., NAGAO S., ITOH K., NAGATA K., MIURA S. Differential expression of CCR5 and CRTH2 on infiltrated cells in colonic mucosa of patients with ulcerative colitis. *J. Gastroenterol. Hepatol.*, 2003, **18** : 1081-1088.
37. ALLEZ M., MAYER L. Regulatory T cells. Peace keepers in the gut. *Inflamm. Bowel Dis*., 2004, **10** : 666-676.
38. MAUL J., LODDENKEMPER C., MUNDT P., BERG E., GIESE T., STALLMACH A., ZEITZ M., DUCHMANN R. Peripheral and intestinal regulatory $CD4^+CD25^{high}$ T cells in inflammatory bowel disease. *Gastroenterology*, 2005, **128** : 1868-1878.
39. BELKAID Y., ROUSE B.T. Natural regulatory T cells in infectious disease. *Nature Immunol*., 2005, **6** : 353-360.
40. KULLBERG M.C., PEARCE E.J., JIENY S.E., SHER A., BERZOFSKY J.A. Infection with *Schistosoma mansoni* alters Th1/Th2 cytokine responses to a non-parasite antigen. *J. Immunol.*, 1992, **148** : 3264-3270.
41. HOGABOAM C.M., VALLANCE B.A., KUMAR A., ADDISON C.L., GRAHAM F.L., GAULDIE J., COLLINS S.M. Therapeutic effects of interleukin-4 gene transfer in experimental inflammatory bowel disease. *J. Clin. Invest*., 1997, **100** : 2766-2776.
42. REARDON C., SANCHEZ A., HOGABOAM C.M., MC KAY D.M. Tapeworm infection reduces epithelial ion transport abnormalities in murine dextran sulfate sodium-induced colitis. *Infect. Immun*., 2001, **69** : 4417-4423.
43. HUNTER M.M., WANG A., HIROTA C.L., MC KAY D.M. Neutralizing anti-IL-10 antibody blocks the protective effect of tapeworm infection in a murine model of chemically induced colitis. *J. Immunol.*, 2005, **174** : 7368-7375.
44. KHAN W.I., BLENNERHASSET P.A., VARGHESE A.K., CHOWDHURY S.K., OMSTED P., DENG Y., COLLINS S.M. Intestinal nematode infection ameliorates experimental colitis in mice. *Infect. Immun*., 2002, **70** : 5931-5937.
45. ELLIOTT D.E., LI J., BLUM A., METWALI A., QADIR K., URBAN J.F. Jr., WEINSTOCK J.V. Exposure to schistosome eggs protects mice from TNBS-induced colitis. *Am. J. Physiol.*, 2003, **284** : G385-391.
46. MOREELS T.G., NIEUWENDIJK R.J., DE MAN J.G., DE WINTER B.Y., HERMAN A.G., VAN MARCK E.A., PELCKMANS P.A. Concurrent infection with *Schistosoma mansoni* attenuates inflammation induced changes in colonic morphology, cytokine levels, and smooth muscle contractility of trinitrobenzene sulphonic acid induced colitis in rats. *Gut*, 2004, **53** : 99-107.
47. ELLIOTT D.E., SETIAWAN T., METWALI A., BLUM A., URBAN J.F. Jr., WEINSTOCK J.V. *Heligmosomoides polygyrus* inhibits established colitis in IL-10-deficient mice. *Eur. J. Immunol.*, 2004, **34** : 2690-2698.
48. SUMMERS R.W., ELLIOTT D.E., WEINSTOCK J.V. Why *Trichuris suis* should prove safe for use in inflammatory bowel diseases. *Inflamm. Bowel Dis.*, 2005, **11** : 783-784.
49. SUMMER R.W., URBAN J., ELLIOTT D., QADIR K., THOMPSON R., WEINSTOCK J. TH2 conditioning by *Trichuris suis* appears safe and effective in modifying the mucosal immune response in inflammatory bowel disease [abstract]. *Gastroenterology*, 1999, **116** : G3592.
50. SUMMERS R.W., ELLIOTT D.E., URBAN J.F. Jr., THOMPSON R, WEINSTOCK J.V. *Trichuris suis* therapy in Crohn's disease. *Gut*, 2005, **54** : 87-90.
51. SUMMERS R.W., ELLIOTT D.E., URBAN J.F. Jr., THOMPSON R., WEINSTOCK J.V. *Trichuris suis* therapy for active ulcerative colitis : a randomized controlled trial. *Gastroenterology*, 2005, **128** : 825-832.
52. FALCONE F.H., PRITCHARD D.I. Parasite role reversal : worms on trial. *Trends Parasitol*., 2005, **21** : 157-160.
53. Radford-Smith G.L. Will worms really cure Crohn's disease ? *Gut*, 2005, **54** : 6-8.
54. VAN KRUININGEN H.J., WEST A.B. Potential danger in the medical use of *Trichuris suis* for the treatment of inflammatory bowel disease. *Inflamm. Bowel Dis.*, 2005, **11** : 515.
55. RAINE T., ZACCONE P., DUNNE D.W., COOKE A. Can helminth antigens be exploited therapeutically to downregulate pathological Th1 responses ? *Curr. Opin. Invest. Drugs*, 2004, **5** : 1184-1191.