

The Report of the NACC Expert
Review Group into the evidence linking
Mycobacterium paratuberculosis
(MAP) and Crohn's Disease

December 2003



National Association for Colitis and Crohn's Disease

Registered Charity No. 282732

Contents

Contents	2
Contributors	3
Introduction and background	4
The current evidence	5
Conclusions and recommendations for further research.....	10
Executive summary.....	12
References	14
Appendix.....	17

© NACC, 2004

National Association for Colitis and Crohn's Disease

4 Beaumont House, Sutton Road, St Albans, Herts. AL1 5HH

Website: www.nacc.org.uk

Registered Charity No. 282732

Report of the NACC Expert Review Group into the evidence linking MAP and Crohn's Disease (December 2003)

Contributors

Chairman

- | | |
|----------------------------------|--|
| Professor Ken Welsh | Visiting Professor in Clinical Genomics
Imperial College
London |
| Professor Paul Hunter | Professor of Health Protection
University of East Anglia
Norwich |
| Dr Jo Colston | Head, Division of Mycobacterial Reseach
National Institute for Medical Research
London

(sadly Dr Jo Colston died early in 2003) |
| Professor Jonathan Rhodes | Professor of Medicine
University of Liverpool
Liverpool |
| Dr Jeremy Sanderson | Consultant Gastroenterologist
Guy's & St Thomas' Hospitals
London |
| Professor Jane Bower | Professor of Entrepreneurial Studies
Strathclyde University |

The first draft of this report was compiled by **Stephen Marchant** of Discovery London.

Introduction and background

Crohn's Disease (CD) is a debilitating and serious inflammatory bowel disease (IBD) of unknown cause. CD has a prevalence of approximately 1 in 1000 people in the UK, and there is some data to suggest that this figure is increasing [1]. Although the disease often responds to medical and surgical treatment, there is no definitive cure. CD represents an important clinical challenge to healthcare professionals and is estimated to cost the NHS between £200 and £320 million pounds per year. If social and economic costs are included the total cost to the nation could be in excess of £600 million per year [2].

There is no agreement as to the aetiology of CD (*the initiating cause of the disease and the process by which it develops*) and several environmental, infective and genetic components to the development of the disease have been suggested over the years. Most experts believe that the development of CD is due to a combination of factors including:

- Genetic predisposition (including the recently described association with the gene NOD2/CARD15)
- Environmental factors (which may include micro-organisms, dietary factors, common chemicals, cigarette smoke or a combination of these)

In recent years several advances have been made in this area, especially in regard to genetics, with several susceptibility genes (*genes that increase the likelihood of developing the disease*) being identified [3]. However, the suggestions made in terms of environmental or infective causes have been more controversial and have not found acceptance, for example the suggested link with the measles virus and MMR vaccine [4]. The only environmental factor that is definitely associated with CD is smoking, in that smokers are more likely to develop the disease and CD patients who smoke are likely to have a poorer clinical course than those who do not [5].

Report of the NACC Expert Review Group into the evidence linking MAP and Crohn's Disease (December 2003)

The evidence for the association between MAP and CD is less clear-cut. Professor Hermon-Taylor and colleagues from St George's Medical School [6-10] have brought the possibility of the bacterium *Mycobacterium paratuberculosis* (MAP) being the cause of CD to the attention of the healthcare and community press, as well as patients. The debate over the validity and implications of this work has continued for some time now and is a cause of concern for patients, healthcare professionals and public health bodies alike. Several reports into the likelihood of an association between MAP and CD have already been completed [2, 11, 12] and the issue has been debated in the House of Lords [13], but all these have failed to agree any firm conclusion other than that the case is unproven.

It is important to note that if the link between MAP and CD is conclusively established there will be a significant public health implication as MAP has been found to enter the human food chain [14-18].

The National Association for Colitis and Crohn's Disease (NACC), the UK - based patient organisation and charity, formed an expert review group in 2002 to consider the available evidence and report back to the Trustees on the following points:

1. *To review the currently published evidence for a link between MAP and Crohn's.*
2. *To consider the likelihood of MAP being a cause of Crohn's disease based on current knowledge.*
3. *To consider what research could be undertaken to answer the question of the relationship of MAP and Crohn's definitively.*

The current evidence

MAP is an aerobic, non-spore forming, non-motile bacillus (bacterium) that is commonly found in the environment. It has been found in cattle and other domestic animals, as well as in wild animals such as rabbits and deer. MAP is

Report of the NACC Expert Review Group into the evidence linking MAP and Crohn's Disease (December 2003)

excreted in large numbers in the faeces of animals infected with the disease and it is also found in the milk of infected animals. In a study of samples taken from milk processing plants MAP has been recently found in approximately 1.8% of pasteurised and 1.6% of unpasteurised samples [19], figures which are similar to those found previously [14-18]. It has been postulated that MAP from the faeces of infected animals will enter the water supply and that it may be present on salad crops, although there is no firm evidence as yet for this. [20].

On the basis of the collected evidence, the review group does not doubt that MAP (both alive and dead) is present in the human diet and is available, *via* foodstuffs and milk, for human consumption.

The UK authorities have already introduced some measures to alter the pasteurisation process and to reduce the presence of MAP in the food chain as a precautionary measure. The effectiveness of these measures has yet to be seen and the impact on public health needs to be assessed. However, these initiatives are to be welcomed.

While it is accepted that MAP enters the food chain, the presence of MAP in the human diet does not prove any causative link between MAP and the development of CD. It is therefore necessary to review how the investigation into this putative association came into being. The suggested link between MAP and CD has arisen for two main reasons.

- First, MAP infection is already known to cause Johne's disease, a Crohn's-like disease in cattle, which has some pathological similarities to the bowel lesions found in CD.
- Secondly, several groups of investigators world-wide have found DNA evidence for MAP infection in samples taken from bowel segments of patients with CD.

MAP and Johne's disease

Johne's disease is endemic in cattle across Europe and the association between MAP and Johne's disease has been known since 1895 [2]. Infection between animals is *via* the faeces and milk and there is often a long incubation period before symptoms develop. A comparison between the clinical and pathological features of CD and Johne's disease is shown in Appendix 1.

The link between MAP and CD

The similarity between CD and Johne's disease was first noted by Dalziel in 1913 [21], but only became seriously investigated after the report by Chiodini et al of successful culture of MAP from two patients with CD [22]. More recently, Hermon-Taylor and colleagues have used a technique called IS900 PCR (*polymerase chain reaction*) to detect MAP DNA in tissue samples from CD patients. Several other laboratories world-wide have found similar results when looking for MAP in the bowel of CD patients using a variety of different methods. In the view of the review group the most notable is a recent, well conducted, study from Ireland that used a laser capture technique to detect MAP DNA in granulomas from a proportion CD patients [23]. This paper concludes '**...that the detection of MAP DNA within granulomas might suggest an infectious aetiology in a subset of patients; alternatively, a transmissible agent may not be involved, but MAP DNA may influence pathogenesis by modifying the local cytokine responses.**'

The variability of the results of the analysis of tissue samples from different centres is still unexplained, with a wide range in the proportion of patients found to have the MAP. We do not know whether the MAP in these Crohn's patients was present in the bowel before the disease began and, if so, whether it caused the CD, or whether having CD makes the bowel more likely to accumulate MAP after the disease has developed. If the latter is correct, we also do not know whether the presence of MAP in the bowel has a deleterious effect on the course of the disease.

Report of the NACC Expert Review Group into the evidence linking MAP and Crohn's Disease (December 2003)

In the majority of controlled studies MAP DNA is also found (at a lower level) in control patients. This reinforces the suggestion that other factors as well as MAP infection (if it is causative) must be involved in the development of CD.

It is apparent that if MAP infection does contribute to the causation of CD, then it is not acting as a conventional infective agent.

Several other bacteria have been (or are being) investigated as being involved in the aetiology of CD. These include *Klebsiella* spp., *Chlamydia* spp., *Eubacterium* spp, *Peptostreptococcus* spp, *Bacteroides fragilis*, *Enterococcus faecalis*, *Escherichia coli*, *Campylobacter jejuni*, *Campylo-bacter faecalis*, *Listeria monocytogenes*, *Brucella abortus*, *Yersinia pseudotuberculosis*, and *Yersinia enterocolitica*. Even assuming that there is an infective component to CD, it cannot be discounted that at least one or more other bacteria could be involved. Moreover it is unclear whether the presence of bacteria within Crohn's disease tissue is part of the causation of the disease or merely a consequence of the disease.

The review group accepts that MAP is present in the bowel of a proportion of patients with CD and also a (lower) proportion of controls [8, 23-36]. The significance of this is unknown and further studies are required to resolve the issue.

MAP in the food chain

There is good evidence to show that MAP can be present in both pasteurised and unpasteurised milk [14, 16]. Indeed, recent figures produced by the Department for Environment, Food and Rural Affairs (DEFRA) show that, paradoxically, in one study that tested 814 samples of milk from 258 dairies (244 samples of raw milk, 567 samples of pasteurised and 3 of UHT milk) more pasteurised milk samples (10, 1.8%) were contaminated with MAP than unpasteurised milk samples (4, 1.6%). [19].

Report of the NACC Expert Review Group into the evidence linking MAP and Crohn's Disease (December 2003)

The review group noted that the Food Standards Agency (FSA) and DEFRA are already implementing guidance to farmers and milk producers with regard to eliminating MAP from milk supplies. As well as milk, there is also concern that MAP may be present in the water supply and contaminating food crops, but the evidence for this is much weaker, and a recent large study did not find MAP in the water supply [37].

Farmers, abattoir staff and veterinary surgeons would be expected to be more exposed to MAP day-to-day, but instead show a reduced incidence of CD [38]. The reason for this is unknown, but it may indicate that they have developed a 'tolerance' for MAP that reduces their risk of developing CD or it may indicate the association between MAP and CD is not causative

Alternatively it is conceivable that environmental contamination with bacteria such as MAP might actually be beneficial by inducing immune tolerance. There is evidence that Crohn's patients are more likely to have had a clean environment in childhood [39].

In general mycobacterial disease is poorly understood. We do know that in other mycobacterial diseases steroid therapy and the newer tumour necrosis factor (TNF alpha) inhibitors (*infliximab*) lead to an increase in the numbers of bacteria and worsening of the disease. This effect is not seen in CD. **On the basis of this, the review group concluded that, if MAP is involved in the aetiology of CD, it is not acting as a conventional infective agent.**

In addition, therapy for CD with anti-mycobacterial drugs has had, at best, equivocal results. The review group agree with the conclusions of the European Commission report, which states '*..there is a small sub-group of people with Crohn's disease who do show clinical improvement, which is occasionally dramatic, in response to treatment with conventional anti-tuberculous chemotherapy. With few exceptions, however, clinical improvement is not lasting and complete cure has not been achieved*' [40]. It

Report of the NACC Expert Review Group into the evidence linking MAP and Crohn's Disease (December 2003)

is important to note that conventional anti-tuberculosis therapy is not effective against MAP. A clinical trial currently being undertaken in Australia will clarify the proportion of CD patients who respond well to anti-MAP drugs and the duration of the improvement.

The review group agreed that the hypothesis that CD has distinct clinical sub-groups is likely to be correct. If MAP is causative, it is likely to be causative to only one subset of the disease and perhaps only to one genetic sub-type. The epidemiological data are not strong enough to prove or disprove this idea, but the review group considered that this would be a sensible focus for further research.

Taking all of the evidence into consideration, the review group is of the opinion that currently a causative association between MAP and CD is unproven.

Conclusions and recommendations for further research

1. On the basis of the current evidence the review group concluded that a causative association between MAP and CD is unproven.
2. If MAP is involved in the aetiology of CD it is not acting as a conventional infective agent.
3. MAP is however present in the bowel of a proportion of patients with CD and also a lower proportion of controls. Whether this is a cause or a consequence of the disease process has yet to be established. Other bacteria are also present in increased numbers in Crohn's disease tissue.
4. The review group notes with approval that the Food Standards Agency and DEFRA are already implementing guidance directed towards the elimination of MAP from milk supplies and have funded research to investigate the possibility of links between CD and water supply.
5. It is obviously of great importance to ascertain the aetiology and pathogenesis of Crohn's disease and this information is vital in potentially

Report of the NACC Expert Review Group into the evidence linking MAP and Crohn's Disease (December 2003)

reducing the risk of developing the disease, its treatment and possible cure. While the hypothesis linking MAP and CD has appropriately received attention, this should not be to the detriment of other equally possible hypotheses.

6. There is not a single definitive study that could be done to prove this hypothesis one way or the other. Evidence needs to be considered from several areas of research: examination of tissue samples, epidemiology and therapeutic trials. At present the only area that has been established to the point where the review group feels that perhaps further research is not needed is the presence of DNA in granulomas.
7. The review group believes that the hypothesis that CD is a collection of different conditions with differing aetiologies, either genetic or environmental, is likely to be correct. If MAP is causative, it could be causative to only one subset of the disease and perhaps only to one genetic sub-type. The review group considered that this would be a fruitful direction for further research.
8. It is recommended that well designed epidemiology studies be performed and that, clinical and genetic sub-sets, data relating to the *NOD2*, disease location, disease type (i.e. Behcet's type, arthropathies, extra-intestinal etc), date of diagnosis and smoking status should be included in the study.
9. Key evidence that could support a causative association between MAP and CD would be lifelong or very prolonged remission in substantial numbers of patients following a course of antibiotic therapy targeted at MAP, preferably given in the context of a double-blind controlled trial. Such trial is under way in Australia and will hopefully report results in early 2005.

Executive summary

1. Crohn's disease (CD) is a debilitating and serious bowel condition that is increasing in incidence. Although the disease often responds to surgical and medical treatment, there is no definitive cure.
2. There is no agreement as to the cause of CD and several hypotheses have been put forward over the years. Most experts believe that a combination of genetic factors, including the recently described association with the gene NOD2/CARD15, and environmental factors contribute to the cause of the disease.
3. Recent evidence for an association with the bacterium *Mycobacterium paratuberculosis* (MAP) has both raised concerns and caused controversy. Doctors are divided as to whether MAP causes CD and several reports into this area have given equivocal answers.
4. To clarify this situation, in 2002, the National Association for Colitis and Crohn's Disease (NACC) instituted an expert review group to evaluate the available evidence and give recommendations for future research. The review group's conclusions and recommendations are summarised below:
5. There is compelling evidence to show that MAP, both alive and dead, is present in human foods. The evidence for this is strongest in milk supplies.
6. DNA from MAP can be found in the bowel tissue of a proportion of patients with CD. However, it is also found in lesser quantities in the bowel tissue of some people who do not have the disease. The significance of this in terms of the cause of CD is unknown.
7. Having reviewed the available evidence, it is concluded that the case for MAP being involved in the causation of CD is so far unproven.
8. Whilst the link between MAP and CD is unproven, the review group welcome the precautionary measures undertaken by the Department for Environment, Food and Agriculture and the Food Standards Agency to reduce the incidence of MAP in the food chain.

Report of the NACC Expert Review Group into the evidence linking MAP and Crohn's Disease (December 2003)

9. There is enough evidence to conclude that CD is not a conventionally infectious disease and that, if there is a microbial component to the causation of the disease, this is not acting as a conventional pathogen.
10. As the case for MAP to be causative in CD is not proven, the review group recommends that further research into the area should include studies that will identify which sub-sets of CD patients, if any, appear to have MAP as a primary cause of their disease. To achieve this aim, clinical and genetic sub-sets of CD patients should be included in future studies.
11. The review group recommends that well designed epidemiology studies be performed which include data on the sub-types of CD.
12. Clearer evidence for the role of MAP in Crohn's disease should become available with the completion of the randomised controlled trial of anti-MAP therapy that is under way in Australia.

Report of the NACC Expert Review Group into the evidence linking MAP and Crohn's Disease (December 2003)

References

1. British Society of Gastroenterology Guidelines (Second Edition, forthcoming 2004).
2. Rubery, E., *A review of the evidence for a link between exposure to mycobacterium paratuberculosis (MAP) and Crohn's disease (CD) in humans - A report for the food standards agency*. 2001, Food Standards Agency: London.
3. Cho, J.H., *Update on the genetics of inflammatory bowel disease*. *Curr Gastroenterol Rep*, 2001. **3**(6): p. 458-63.
4. Kugathasan, S., *MMR and IBD: the only thing we have to fear is...fear itself*. *Inflamm Bowel Dis*, 2001. **7**(4): p. 349-50.
5. Cosnes, J. et al., *Effects of smoking on the long-term course of Crohn's Disease*. *Gastroenterology*, 1996. **110**: p. 424-31.
6. Hermon-Taylor, J., *Causation of Crohn's disease: the impact of clusters*. *Gastroenterology*, 1993. **104**(2): p. 643-6.
7. Hermon-Taylor, J., *The causation of Crohn's disease and treatment with antimicrobial drugs*. *Ital J Gastroenterol Hepatol*, 1998. **30**(6): p. 607-10.
8. Hermon-Taylor, J., et al., *Causation of Crohn's disease by Mycobacterium avium subspecies paratuberculosis*. *Can J Gastroenterol*, 2000. **14**(6): p. 521-39.
9. Hermon-Taylor, J., *Protagonist. Mycobacterium avium subspecies paratuberculosis is a cause of Crohn's disease*. *Gut*, 2001. **49**(6): p. 755-6.
10. Hermon-Taylor, J. and T. Bull, *Crohn's disease caused by Mycobacterium avium subspecies paratuberculosis: a public health tragedy whose resolution is long overdue*. *J Med Microbiol*, 2002. **51**(1): p. 3-6.
11. Cormican, M., *Mycobacterium paratuberculosis - does it contribute to Crohn's disease*. 2000, Food Safety Authority of Ireland: Dublin.
12. Welfare, S.C.o.A.H.a.A., *Possible link between Crohn's disease and paratuberculosis*. 2000, European Commission: Brussels.
13. HANSARD. 2000, House of Lords: London.
14. Grant, I.R., et al., *Incidence of Mycobacterium paratuberculosis in raw sheep and goats' milk in England, Wales and Northern Ireland*. *Vet Microbiol*, 2001. **79**(2): p. 123-31.
15. Grant, I.R., et al., *Effect of commercial-scale high-temperature, short-time pasteurization on the viability of Mycobacterium paratuberculosis in naturally infected cows' milk*. *Appl Environ Microbiol*, 2002. **68**(2): p. 602-7.
16. Grant, I.R., H.J. Ball, and M.T. Rowe, *Incidence of Mycobacterium paratuberculosis in bulk raw and commercially pasteurized cows' milk from approved dairy processing establishments in the United Kingdom*. *Appl Environ Microbiol*, 2002. **68**(5): p. 2428-35.

Report of the NACC Expert Review Group into the evidence linking MAP and Crohn's Disease (December 2003)

17. Grant, I.R., H.J. Ball, and M.T. Rowe, *Isolation of Mycobacterium paratuberculosis from milk by immunomagnetic separation*. Appl Environ Microbiol, 1998. **64**(9): p. 3153-8.
18. Grant, I.R., *Does Mycobacterium paratuberculosis survive current pasteurization conditions?* Appl Environ Microbiol, 1998. **64**(7): p. 2760-1.
19. Food Standards Agency: National Study on the Microbiological Quality and Heat processing of Cow's Milk (http://www.foodstandards.gov.uk/science/sciencetopics/microbiology/mapinmilk/MAP_results) website accessed 8th December 2003.
20. Whan, L.B., et al., *Bactericidal effect of chlorine on Mycobacterium paratuberculosis in drinking water*. Lett Appl Microbiol, 2001. **33**(3): p. 227-31.
21. Dalziel T. Chronic interstitial enteritis. Brit Med J 1913;2:1068-70.
22. Chiodini et al, Possible role of mycobacteria in inflammatory bowel disease. I. An unclassified Mycobacterium species isolated from patients with Crohn's disease. Dig Dis Sci 1984;29:1073-9.
23. Ryan, P., et al., *PCR detection of Mycobacterium paratuberculosis in Crohn's disease granulomas isolated by laser capture microdissection*. Gut, 2002. **51**(5): p. 665-70.
24. Naser, S.A., et al., *In situ identification of mycobacteria in Crohn's disease patient tissue using confocal scanning laser microscopy*. Mol Cell Probes, 2002. **16**(1): p. 41-8.
25. Chiodini, R.J., et al., *Characteristics of an unclassified Mycobacterium species isolated from patients with Crohn's disease*. J Clin Microbiol, 1984. **20**(5): p. 966-71.
26. Sanderson, J.D., et al., *Mycobacterium paratuberculosis DNA in Crohn's disease tissue*. Gut, 1992. **33**(7): p. 890-6.
27. Thorel, M.F., *Relationship between Mycobacterium avium, M. paratuberculosis and mycobacteria associated with Crohn's disease*. Ann Rech Vet, 1989. **20**(4): p. 417-29.
28. Dell'Isola, B., et al., *Detection of Mycobacterium paratuberculosis by polymerase chain reaction in children with Crohn's disease*. J Infect Dis, 1994. **169**(2): p. 449-51.
29. Lisby, G., et al., *Mycobacterium paratuberculosis in intestinal tissue from patients with Crohn's disease demonstrated by a nested primer polymerase chain reaction*. Scand J Gastroenterol, 1994. **29**(10): p. 923-9.
30. Fidler, H.M., et al., *Specific detection of Mycobacterium paratuberculosis DNA associated with granulomatous tissue in Crohn's disease*. Gut, 1994. **35**(4): p. 506-10.
31. Murray, A., et al., *Mycobacterium paratuberculosis and inflammatory bowel disease: frequency distribution in serial colonoscopic biopsies using the polymerase chain reaction*. Microbios, 1995. **83**(337): p. 217-28.
32. Suenaga, K., et al., *Mycobacteria in the intestine of Japanese patients with inflammatory bowel disease*. Am J Gastroenterol, 1995. **90**(1): p. 76-80.

Report of the NACC Expert Review Group into the evidence linking MAP and Crohn's Disease (December 2003)

33. Erasmus, D.L., et al., *Mycobacterium paratuberculosis and Crohn's disease*. Gut, 1995. **36**(6): p. 942.
34. Gan, H., et al., *Mycobacterium paratuberculosis in the intestine of patients with Crohn's disease*. Zhonghua Nei Ke Za Zhi, 1997. **36**(4): p. 228-30.
35. Mishina, D., et al., *On the etiology of Crohn disease*. Proc Natl Acad Sci U S A, 1996. **93**(18): p. 9816-20.
36. Tiveljung, A., et al., *Presence of eubacteria in biopsies from Crohn's disease inflammatory lesions as determined by 16S rRNA gene-based PCR*. J Med Microbiol, 1999. **48**(3): p. 263-8.
37. Hunter P, et al.. 2001. *Fate of Mycobacterium avium complex in Drinking Water Treatment and Distribution Systems (DWI0815)*. Drinking Water Inspectorate, London.
38. Verbal communication.
39. Gent, AE, et al., *Inflammatory bowel disease and domestic hygiene in infancy*. Lancet, 1994. 343: p. 766-67.
40. European Commission, Report of the Scientific Committee on Animal Health and Animal Welfare (Adopted 21st March 2000): *Possible links between Crohn's Disease and Paratuberculosis*. SANCO/B3/R316/2000 p. 47

Report of the NACC Expert Review Group into the evidence linking MAP and Crohn's Disease (December 2003)

Appendix

Clinical features of Crohn's disease and Johne's disease

	CD	Johne's disease
Preclinical		
– Signs and Symptoms	Unknown	Decreased milk yield
– Incubation period	Unknown	> 6 months
Clinical stage		
– symptoms at presentation	Chronic diarrhoea Abdominal pain Weight loss	Chronic diarrhoea Dull coat Weight loss Decreased milk yield
GI symptoms		
– diarrhoea	Chronic	Chronic
– blood on the stool	Rare	Rare
– vomiting	Rare	No
– abdominal pain	Yes	Unknown
– bowel obstruction	Yes	No
– fistulae	Yes	No
Extra-intestinal		
– polyarthritis/arthropathy	Yes	No
– uveitis	Yes	No
– skin lesions	Yes	No
– amyloidosis	Yes	No
– hepatic granulomatosis	Yes	Yes
– renal involvement	Yes	No
Clinical course	Relapsing/remitting	Relapsing/remitting

Report of the NACC Expert Review Group into the evidence linking MAP and Crohn's Disease (December 2003)

Pathological features of Crohn's disease and Johne's disease

	CD	Johne's disease
Lesion location		
oesophagus and oral cavity	Yes	No
ileum and colon	Yes	Yes (ileum and jejunum are initial and most frequent locations)
mesenteric lymph nodes	Yes	Yes
rectum, anus	Yes (not always)	In advanced disease
segmental	Yes	Yes
Macroscopic Features		
macroscopic appearance	Oedema of bowel wall	Thickened bowel wall
parietal oedema	Yes	Yes
stenosis	Yes	Rare
perforation	Yes	Rare
fistula	Yes	No
pseudopolyps	Yes	No
mucosal aspect	'Cobble stone'	Corrugated (not always in sheep)
Microscopic appearance		
transmural involvement	Yes	Yes
fibrosis	Yes	No
lymphoid aggregates	Yes	Yes
granuloma	Yes (50–70%)	Yes
caseation	No	Usually not
fissures	Yes	No
visible acid fast bacilli	No	Yes