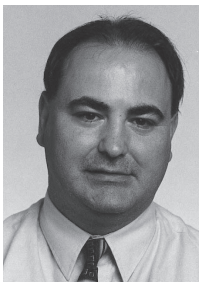
海外特別講演

George T. Macfarlane, Ph.D

Professor of Bacteriology,
University of Dundee, Microbiology and Gut Biology Group,
Ninewells Hospital Medical School, Dundee DD1 9SY, UK



Background:

The speaker is a microbiologist who has worked on various aspects of the human intestinal microbiota for 30 years. His initial work with the Medical Research Council in the 1980s involved studies on resistant starch and polysaccharide breakdown by gut bacteria, together with investigations on *in vitro* modelling, proteolysis, and hydrogen metabolism, particularly in relation to dissimilatory sulphate reduction. Subsequently, investigations were undertaken on prebiotics, ageing, and bacterial biofilms in the gastrointestinal tract. After moving to the University of Dundee in 1999, research focused on mucosal bacterial communities in IBD, and their structural modification with synbiotics and antibiotics. Current projects involve modelling bacterial biofilms and cellular interactions in Barrett's oesophagus, as well as studies on *Clostridium difficile*

Research interests:

Human colonic bacteria: ecology, physiology and pathogenicity
Ageing and the intestinal microbiota
Environmental regulation of virulence determinants in pathogenic microorganisms
Growth and metabolic activities of intestinal bacteria on mucosal surfaces and biofilms
Bacterial involvement in inflammatory bowel disease and cancer
Probiotics and prebiotics

Positions:

1984–1994: Medical Research Council Career Research Scientist, Dunn Clinical Nutrition Centre (DCNC), Cambridge
1994–1999: MRC Senior Research Scientist (DCNC)
1999–2001: Senior lecturer, The University of Dundee
2001–2013: Appointed to a Personal Chair in Bacteriology, The University of Dundee

Other work

1987–1992: Editorial Board Member, *Journal of Applied Bacteriology*
1992–1996: Senior Editor, *Journal of Applied Bacteriology*
1999–2014: Associate Editor, *Journal of Applied Microbiology*
1999–2014: Associate Editor, *Letters in Applied Microbiology*
2004–2008: Editor, *Biofilms*
2002–2011: Editorial Board Member, *Applied and Environmental Microbiology*
2011–2015: Editor, *Applied and Environmental Microbiology*

Since 2001: Member of 19 national and international research assessment and grant awarding committees
Invited speaker at 50 national and international scientific conferences
Author or co-author of 76 publications

Professional memberships

Society for General Microbiology, Society for Applied Microbiology, American Society for Microbiology, British Society for Gastroenterology, Pathological Society, Fellow of the Society of Biology, Fellow of the Royal Society of Medicine

Ecology of intestinal microorganisms in health and disease

George T. Macfarlane
University of Dundee, Microbiology and Gut Biology Group,
Ninewells Hospital Medical School

This presentation will focus on the role of intestinal bacteria in colon cancer, and inflammatory bowel diseases (IBD) such as ulcerative colitis (UC) and Crohn's disease (CD), as well as conditions in the upper gut, such as bacterial overgrowth in patients receiving enteral nutrition (EN), as well as Barrett's oesophagus and oesophageal adenocarcinoma.

Intestinal microorganisms play a major role in human physiology. Until relatively recently, most work has focused on luminal contents in the large bowel, however, there is increasing evidence that mucosal surfaces are heavily colonised throughout the digestive tract, including the upper gut in various disease states, although the species composition and microbial load is normally much lower in this region of the digestive tract. Despite this, dysbiosis associated with upper gut colonisation can cause major health problems.

Barrett's oesophagus (BO) is a complication of chronic gastro-oesophageal reflux disease, in which individuals have a greatly increased risk of adenocarcinoma. To investigate whether microbial biofilm communities might play a role in the disease process, bacterial populations in oesophageal aspirates, and oesophageal mucosae of BO patients were studied, together with healthy controls. Confocal microscopy was also used to determine the spatial localisation of these organisms on mucosal surfaces. Overall, 46 bacterial species belonging to 16 genera were detected by culturing, with 10 species being common to both subject groups. Both aspirate and biopsy samples from BO patients contained complex microbial communities. Interestingly, high levels of campylobacters (*C. concisus*, *C. rectus*), were found in BO patients, but not in non-diseased controls. Microscopy showed that mucosal bacteria were often present in microcolonies. The presence of pathogenic campylobacters in people with BO may suggest a link either in the initiation, maintenance or exacerbation of the disease processes leading to adenocarcinoma formation. Interactions of *C. concisus* and Barrett's cell lines *in vitro* show that these bacteria interfere with signalling factors (e.g. COX2, CDX1, P53) at a number of points in the cell cycle, while these effects are not seen with the commensal bacterium *Streptococcus salivarius*.

In healthy people, the small bowel is normally sparsely populated by microorganisms. This is due, in part, to the rapid flow of digestive materials through the gut, which prevents the establishment of permanent communities. However, during enteral feeding via percutaneous endoscopic gastrostomy tubes, innate defence mechanisms in the upper gut are bypassed, resulting in microbial overgrowth. The effects of EN on mucosal colonisation, and the gut-associated immune system, are not well understood, but studies on surface-associated microbial populations in the gastric and duodenal mucosae of patients receiving EN showed that there were significantly higher levels of bacterial DNA in mucosal biopsies from both sites in these individuals, compared to control subjects. The main organisms found were staphylococci and enterobacteria. Allied to this, the expression of pro-inflammatory cytokines such as IL1-α, IL6 and TNF-α, was significantly higher in gastric and

small intestinal mucosae from patients fed normal diets, in comparison with those receiving EN. These studies demonstrated that EN resulted in significant bacterial overgrowth in the upper gut, and paradoxically, reduced pro-inflammatory cytokine responses, which may facilitate spread of the organisms through the body.

Investigations on the large gut have shown that the bowel wall is heavily colonised by diverse and highly complex bacterial communities. Healthy mucosal tissue from different regions of the large bowel were obtained from 26 patients undergoing emergency resection of the colon, and used to study mucosal biofilm communities in the distal gut. Quantitative bacteriological measurements were done by qPCR. Mucosal bacteria were also visualised using confocal microscopy. Mucosal cell population densities were highest in the terminal ileum, while there was no significant difference in overall bacterial numbers in different parts of the colon. Bifidobacteria were more important in the large bowel than in the terminal ileum, while lactobacilli were more prominent in the distal colon. *Eubacterium rectale* occurred in higher numbers in the ascending colon while *Faecalibacterium prausnitzii* was more significant in the proximal and descending colon. Mucosal-associated bacterial diversity was host-dependent in that considerable inter-individual variation was observed. However, studies in cancer patients showed differential colonisation of tumour sites and healthy tissues, with bacteroides and enterobacteria predominating on the tumours, and bifidobacteria occurring to a greater extent in non-diseased tissues.

The aetiologies of inflammatory bowel diseases such as UC and CD are unclear, but it is believed that intestinal bacteria are involved in some way in these dysbiotic processes. Both viable counting and molecular analyses of rectal biopsies have shown that marked differences exist in some bacterial communities, particularly bifidobacteria, which are present in much lower numbers on mucosal surfaces. Whether this is simply due to local environmental changes caused by the disease, or is linked to disease initiation is unclear. However, feeding studies in both UC and CD patients with a *Bifidobacterium longum*/inulin/fructo-oligosaccharide synbiotic have been shown to increase bifidobacterial numbers and diversity in both forms of IBD, with concomitant relief of tissue inflammation and disease symptoms.