SPECIAL ARTICLE

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The appendix-mucosal immunity and tolerance in the gut: consequences for the syndromes of appendicitis and its epidemiology

Alan de Costa

College of Medicine and Dentistry, James Cook University, Cairns Clinical School, Cairns Hospital, Cairns, Queensland, Australia

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Correspondence
A/Prof Alan de Costa, College of Medicine and Dentistry, James Cook University, Cairns Clinical School, Cairns Hospital, Cairns, QLD 4870, Australia. Email: alan.decosta@jcu.edu.au

A. de Costa FRACS, FRCSI.

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Abstract

The cause of appendicitis is unknown. A review is presented across diverse sources relating to the biology of the appendix and its perturbations. A mechanistic model of the function of the appendix is presented, and its application to the syndromes and consequences of appendicitis is described.

Introduction

Since the start of the millennium, the work of The Human Microbiome Project has transformed our understanding of human physiology. The tools of metagenomics show the number of genes in the gut to vastly outnumber the human genome. Metrics used to describe the microbiota relating to diversity, richness, depletion and abundance, among other attributes, allow description of different phenotypes. This microbial array collectively interacts with the gut and its contents to provide unique metabolic functions of vital importance to the individual.[1] Most of the organisms in the gastrointestinal tract, the microbiota, are pathogenic given opportunity and context.[2,3] Immunity and tolerance across epithelial surfaces in the gut have relevance to inflammatory gut disease, including in the appendix.

Tolerance and immunity in the gut

The mature gut microbiota is dominated by two phyla that make up 90% of all organisms, the Firmicutes and Bacteroidetes, both phyla include obligate anaerobes.[1,2] Proteobacteriaceae contains the family Enterobacteriaceae, of which the familiar coliforms are facultative anaerobes.

Interactions occur in the first instance between the microbiota, diet and the immunological tissues in the gut (gastrointestinal-associated lymphatic tissue, GALT) across the epithelial surface, harmoniously in a 'steady state', and with inflammatory responses when not, a condition regarded as 'dysbiosis'.[3–5] Symbiotic evolution of microbe, diet and gut over millennia is now challenged by modernity, as an epidemic of non-infectious intestinal disease has replaced the gut infections of the past.[4,6–9]

The Hygiene Hypothesis[10,11] allowed an explanation of reactive inflammatory phenomena to environmental antigens. This has since been extended by 'The Old Friends Hypothesis'[12] which provides a basis for understanding immunological tolerance of relevance in the gut.

Mechanisms of immunity and tolerance in the gut

A single layer of epithelial cells held together by tight junctions separates a profusion of organisms from the lamina propria[2–4] (Fig. 1). Interaction between organisms and the epithelium may result in inflammatory responses. Both 'immunity' and 'tolerance' are required in the steady state.[6]

Mucus is produced in the goblet cells in the epithelium. This is designated as MUC2[2,13,14] in the colon, and consists of complex glycopeptide layers: the inner layer is adherent to the epithelium as a glyco-calyx, and the outer layer less so.[13] The glycopeptide side chains produce a three-dimensional mucus barrier resembling a glyco-code,[2,13,14] which may allow preferential access to some organisms.[2] The outer mucus contains collections of organisms in biofilms,[15,16] which can be detached to renew the microbiota following infectious enteritis or antibiotics, but can also be

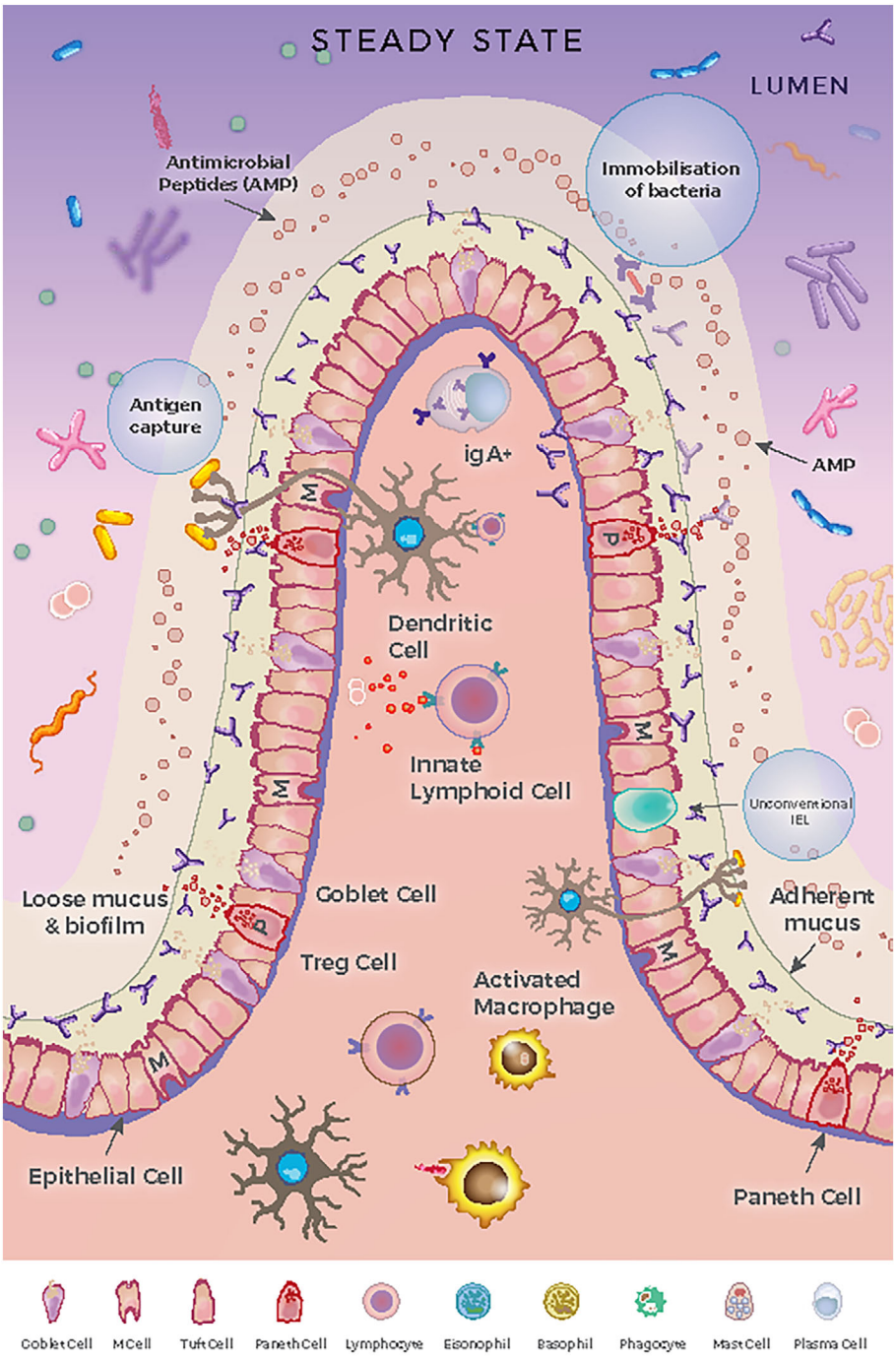

Fig. 1. Steady state.

associated with neoplastic risk.[17] Paneth cells in the crypts produce an array of antimicrobial peptides which form a gradient in the mucus and help to keep organisms at a distance.[2,13] IgA produced by plasma cells in the lamina propria is exocytosed by the epithelial cells into the mucus. IgA immobilizes bacteria and prepares them for opsonization. IgA does not fix complement[3] and this is not an inflammatory process. Some of these interactions are demonstrated in Figure 1.[2,3,13] A complex interplay occurs between microbiota and mucus layers,[13,14] while obligate gut pathogens have evolved particular mechanisms to evade these defences.[2] Dietary fibre provides an important carbon source for the microbiota. These undigested complex carbohydrates are fermented by the microbiota in the colon producing short-chain fatty acids, which are in turn a carbon source for the epithelial cells.[2] When fibre is diminished in the diet, the microbiota may turn to the mucus layers as a carbon source degrading them.[13,18] The mucus layers may be depleted by the ubiquitous accompaniments of modernity as well; detergents, emulsifiers, petrochemical fumes as well as infectious gastroenteritis.[4] As mucus layers are degraded, deeper defences are exposed.

Beneath the epithelial layers, innate and adaptive immune mechanisms constitute another layer of defence.[16] Innate immunity, featuring monocytes and macrophages, an ancient system of immunity present in invertebrates, responds immediately and powerfully to invasion and is non-specific.[19]

Naïve lymphocytes and T cells are activated in many ways through dendritic cell capture of antigens or through antigen presentation at microfold cells. Activated in this way, cells travel to GALT and mesenteric lymph nodes and induce clonal selection. The cells are imprinted with their tissue of origin, and are primed to return to the site of antigenic exposure.[3,16] These clones of T cells and B cells previously selected and expanded by antigen presentation are memory cells and respond precisely to the antigens to which they have been previously exposed. The process of selection may take a week, while response after re-challenge is immediate and specific.[20]

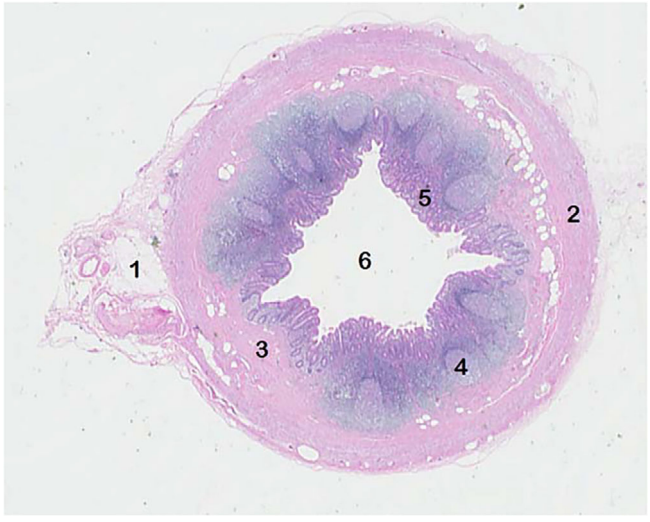

Fig. 2. Transverse section of a healthy adult appendix. 1, Mesoappendix; 2, muscularis externa; 3, submucosa; 4, lymphoid follicle; 5, mucosa; 6, lumen.

While innate and adaptive processes were once considered quite separate, recent work suggests that this separation is less clear cut.[21,22]

In the steady state, the balance in the lamina propria is anti-inflammatory driven by Treg cell expression. The 'old friends' are selected by the sensory and effector patterns across the epithelium through the collections of immunological cells in the lamina propria, lymphatic collections, Peyer's patches and the appendix.[23]

Monocytes express many kinds of pattern recognition receptors. Toll-like receptors and NOD-like receptors among others recognize pathogen-associated molecular patterns on organisms following bacterial uptake, across particularly microfold cells in the epithelium.[24] These can also learn to recognize and react to novel antigens, and initiate Th17 inflammatory responses.[21] These innate 'memory' mechanisms have the potential for producing epigenetic modelling and phenotypic change. Dendritic cells in the lamina propria sample commensals (old friends) in the lumen to expand populations of regulatory T cells, or switch to effector phenotypes that preferentially drive anti-inflammatory processes.[12]

Damage to mucus barriers may also predispose to 'leaky gut' and associations varying from irritable bowel syndrome and type 2 diabetes to Alzheimer's disease.[24,25]

The appendix: special considerations

In embryology, the appendix develops close to the apex of the midgut loop in the physiological hernia within the vitello-intestinal

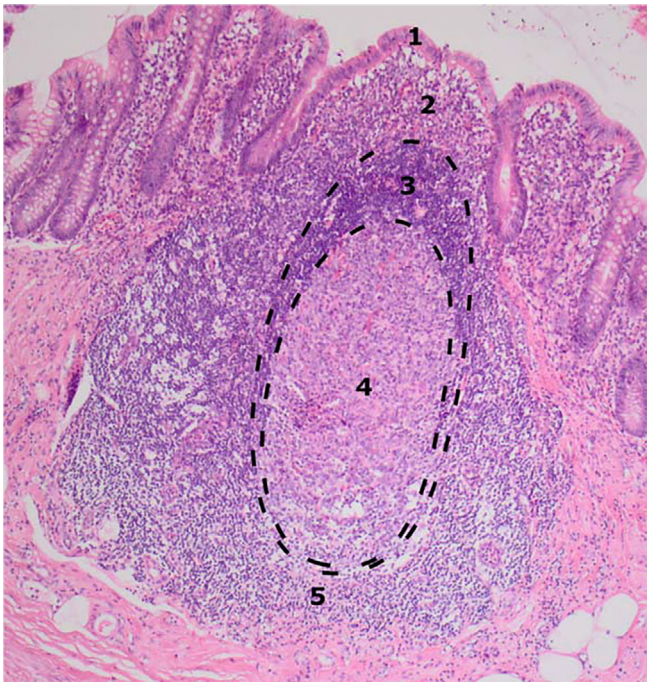

Fig. 3. The functional unit of the appendix: the appendiceal lymphoid follicle. Indicated are the distinctive areas of its most important constituents. 1, Dome epithelium: intraepithelial lymphocytes; 2, mixed cell zone: T lymphocytes, B lymphocytes, macrophages; 3, mantle zone: small B lymphocytes; 4, % germinal centre: centroblasts, centrocytes, follicular dendritic cells, macrophages; 5, T-cell area: T lymphocytes, macrophages.

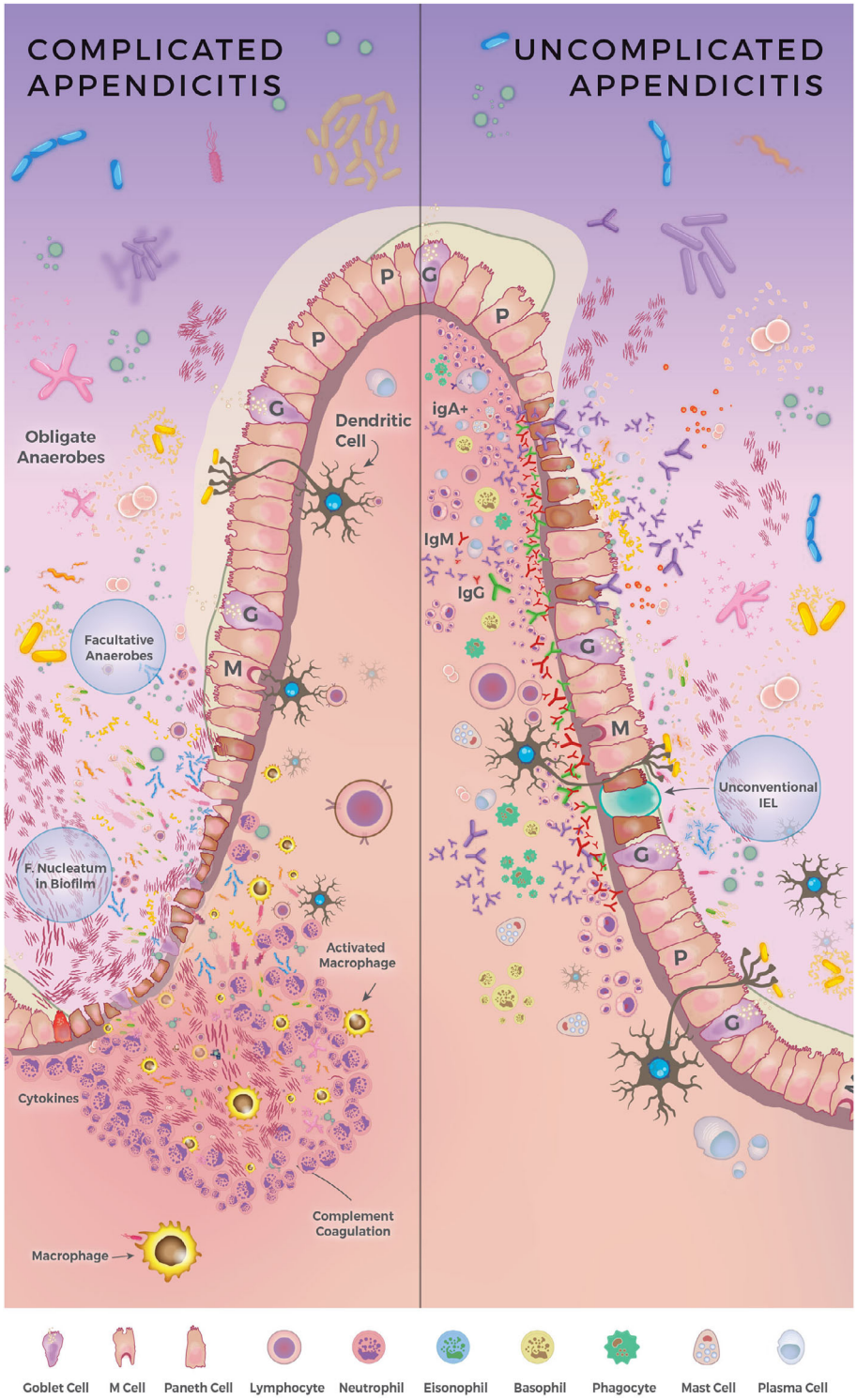

Fig. 4. Complicated and uncomplicated appendicitis.

duct, which returns into the abdomen following particular rotations at about week 10, into its adult position.[26] By week 17, lymphocytes are seen to accumulate in the appendix.[7]

The normal human foetus at birth has a sterile intestine, which is rapidly colonized by vaginal organisms and from breast feeding. This developing microbiota is initially occupied by facultative anaerobes,[7] but within weeks begins to resemble the adult microbiota which are essentially anaerobic.[7,23] Complete maturity of the microbiota is thought to occur at about 3 years, evolving together with the immunological tissue in the gut[7,16,23] as a basis for 'old friends'. Figures 2 and 3 demonstrate the intensity of the mucosal immune toolkit of the appendix, and its intimacy across the dome epithelium with the lumen and its contents.[16]

When the surgeon recreates the physiological hernia when mobilizing the right colon and small bowel mesentery (Braasch-Cattel manoeuvre), the appendix, a secondary lymphoid organ, is seen at the apex of afferent loops of small bowel containing increasing concentrations of organisms, and an efferent loop of colon containing the dense colonic microbiota. These midgut loops are based on a vascular supply, the superior mesenteric vessels and lymphatics.[26] Embryology, anatomy, form and structure (Figs 1–3) suggest function. It is likely the role of the appendix is to function as the site of development of immunity and tolerance in the midgut, similar to the function of the thymus in central immunity and tolerance. Functions at both sites are completed by age 3. This function clearly has selective value in the evolution of the human appendix.[7,15,23] Redundancy for this function is provided by Peyer's patches[23] in the small bowel and lymphatic follicles in the large bowel.

Clinical patterns of appendicitis

Surgeons are indebted to the work of Andersson,[27] who showed that there are two clinical patterns of appendicitis, complicated (CA) and uncomplicated (UA), and that one does not usually develop into the other.[28,29] This concept has been incorporated into management guidelines,[30,31] and has provided the basis for the randomized controlled trials (RCTs) and meta-analyses of antibiotic management of UA. Understandably, this antibiotic approach seems to have been popularized since the Covid-19 pandemic.[29]

Failure of the first layer of the epithelial barrier, the mucus layers, produces inflammatory consequences. A contracted Western microbiota is likely to come with a depleted fibre component. It may also allow opportunistic colonization of the niche of the appendix.

While Figure 1 shows an intact mucus layer in the steady state, Figure 4 shows a degraded mucus layer, where organisms can now interact with the epithelium and cause inflammation.

There is good evidence that Fusobacteria, particularly *Fusobacterium nucleatum/necrophorum*, symbionts in the mouth[32] may opportunistically colonize and invade the appendix causing acute inflammation.[33–35] *35 Fusobacterium nucleatum* is a biofilm former[32] and may evade immune mechanisms in the appendix and elsewhere. This process, although led by Fusobacteria in a proportion of cases,[33–35] is polymicrobial, producing an immediate innate inflammatory response.

Figure 4 (left) shows a column of invasive Fusobacteria, approaching the mucus-depleted epithelium, destroying it and making an epithelial defect. This allows coliforms, facultative anaerobes selected by oxygen stress, to stream into the submucosa.[33,34] The inflammatory response is immediate causing macrophage activation and complement and kinin cascades, resulting in an innate inflammatory response. This response may cause sterile resolution, may form a mass or abscess or produce a perforation. It is also a sensitizing event. Bacteroidetes will occupy an abscess when anaerobic conditions are established. The clinical co-relation of this process is of CA. Several reports confirm innate inflammatory antibacterial processes occurring associated with perforating or gangrenous appendicitis.[36–40] The characteristics of the appendix, easily obstructed by swelling in a closed segment, with arteries at risk of thrombotic occlusion provide further context for gangrene and perforation.

These patterns are also reflected in clinical presentations and scoring systems.[31] High scores are associated with a short history and systemic inflammatory phenomena, following rapid complement activation.

This is also a clear and hardly arguable indication for broad-spectrum antibiotics in the context of a threatened or actual perforation and peritonitis (CA). When surgery is unavailable or delayed, this option is then the only one available.[41] The treatment of appendix mass and abscess with antibiotics is uncontroversial.

Figure 4 (right) shows organisms interacting with lymphocytes in the lamina propria. Cytotoxic T cells, B cells and plasma cells producing antibodies are produced immediately; an anamnestic response to 'old friends' or previous sensitizing events. These responses produce histological changes that are described as chronic appendicitis, resolving or focal appendicitis. A wide variety of leucocytes may be seen infiltrating the appendix on histology.[42–47] This is UA, which is here seen to be inflammatory. Gene expression studies raise the possibility that these patterns may represent viral infection in UA, as opposed to bacterial infection in CA.[40]

The clinical distinction between CA and UA is sometimes problematic, and imaging then becomes necessary.[31] Gene expression studies in time may produce markers to help differentiate CA from UA.[40]

Antibiotic treatments for UA have been the subject of numerous RCTs, systematic reviews and meta-analyses,[48–51] and are included in treatment guidelines.[31] Features of these RCTs include a wide array, dose and duration of antibiotics and a low rate of perforation in the antibiotic treatment arms (UA does not become CA[27–29]). This, when combined with the single RCT with a placebo arm

Table 1 Immune response, inflammatory pattern and associations

	Cause	History	Inflammatory pathways	Scoring systems	Associations
Complicated appendicitis[27–29,31] Perforating, gangrenous	Invasive bacterial	<1 day	Innate[36-40]	High[41]	Crohn's disease[59]
	Fusobacteria polymicrobial[32-35]			SIRS+	Colon cancer and appendicitis[60-68]
Uncomplicated appendicitis[29,31,40,42-45,49] Purulent, chronic, focal recurrent	Inflammatory[40,44-47,54]	>1 day	Adaptive[40,42-47]	Low[31]	Chronic ulcerative colitis[54-58,66] Cancer related to Fusobacteria[32,67,68]
	Viral[40,43]			SIRS−	

SIRS, systemic inflammatory response.

showing no difference between antibiotic and placebo,[52] suggests that UA is an inflammatory or possibly anti-viral process.[40] Long-term follow-up at 7 years reports a 39% incidence of recurrent appendicitis.[53] CA, on the other hand, may respond completely to antibiotic, or partially and present as UA.

Antibiotic treatments for UA, although strongly supported,[30] are at odds with the principles of antibiotic stewardship, may not influence the course of the disease and pose long-term inflammatory risk. Further RCTs using a placebo arm, and with long-term follow-up, are warranted.

It has been suggested that the appendix is a 'priming site' for ulcerative colitis,[54–58] and an association of Crohn's disease to perforating appendicitis is reported.[59]

Chronic inflammatory phenomena in the colon are well understood to pose neoplastic risk.[60] In chronic ulcerative colitis, the incidence rate ratio (IRR) for colon cancer is 2.75 (CI 1.9–3.9), with Crohn's IRR of 2.64 (CI 1.69–4.1). Inflammatory processes in the appendix may pose similar risks as well,[61–65] particularly in the context of UA and antibiotic therapy,[64,65] where the appendix remains intact and retained in the abdomen. *Fusobacterium nucleatum* is associated with inflammatory bowel disease[66] and with colon cancer, which may be related to its occurrence in biofilms in and beyond the appendix.[67,68] These relationships are summarized in Table 1.

Reflections on the epidemiology of appendicitis

The incidence of appendicitis has changed dramatically in a hundred years. In 1940, the incidence in New York was 383 per 100 000. The incidence across the USA over the last 20 years is 80 per 100 000. These changes are similar across Northern Europe. In the developing world, rates are seen to be increasing rapidly where there are good data.[69] Within the USA, the rates of appendicitis recently studied in Washington State showed a non-random distribution closely related to socio-economic status. A college degree and a certain income were associated with lower rates of appendicitis, particularly for UA.[70] Whatever the impact of urbanization and modernity, its outcomes may be unequal. These trends may have underlying inflammatory molecular mechanisms producing epigenetic change, and varying population phenotypes.

The risks that modernity presents to homeostasis in the gut are hinted at, but not defined.[4,24] The broad view of epidemiology and the focused tools of immunology may eventually provide us a clearer insight into how we are to live in this world. Much more needs to be done.[71]

The appendix meanwhile will remain a bellwether in our gut reflecting the state of our relationship with old friends and new.

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Conflict of interest

None declared.

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