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Editorial

The Bug is a Feature Pt 4: Good Fences Make Good Neighbors

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Figure 1

'Good fences' is lifted, of course, from Robert Frost's sinewy poem Mending Wall. Written in 1914, as fences were starting to fall across Europe, Africa and the Middle East, it reflects an elemental truth. Diversity may or may not be strength but division definitely is definition, identity, integrity and function. And so it is in us.

We and our microbiota are co-dependent. We are not the same. The barriers between us divide us, define us and engender a relationship which benefits both parties.

We allow those barriers to decay at our peril. The gut epithelial barrier, the largest interface between us and the outside world, is an important example - and one that is increasingly breaking down.

Acting as a complex filter, it allows entry to a range of nutrients via a diverse set of uptake mechanisms, bars very many different types of microbes, antigens and toxins, and produces an array of locally and distally acting messengers which mediate between us and the exterior world. This hugely complex arrangement can be disrupted by infection, antibiotics, intensive exercise [1,2], likely involving glutamine shift [2] and many other factors including dietary change.

The modern diet, which is inter alia depleted in prebiotic fibers, polyphenols and omega 3 PUFA's, and which directly causes dysbiosis and disruption of the gut epithelial barrier, is driving the currently rising tide of GI problems. The relative absence of environmental symbionts may not affect the barrier directly but is surely making the situation worse.

Let's start with the mucous layer, the slime or more correctly gel that overlies our colonocytes; not to be confused with the mucosa, the outer layer of the gut which, among other things, produces the mucous.

Mucous is basically a hydrated and cross-linked network of mucins, structural glycoproteins secreted by goblet cells scattered among the colonocytes. In health, the thickness of the mucous layer must be maintained within a fairly narrow range; too thick, and absorption of nutrients will be slowed, too thin and enterobacteria will come close enough to the colonocytes to trigger excessive inflammatory stress.

It seems reasonable to assume some sort of monitoring / effector system operating to keep mucin production in step with mucin degradation [3], whether this is caused by host proteases [4] or by fluxes of mucolytic enterobacteria. And it seems likely that the substantial historical fall in our intakes of prebiotic fibers [5], which reduces gram positive, saccharolytic bacterial species in the large bowel, has enabled a shift towards gram negative, proteolytic species [6] which on the one hand cause excessive mucin breakdown [7] and on the other, can drive mucin production [1] to the point of exhausting local mucin stores [8,9].

It is likely the overall effect on mucin economics that is important. Probiotic *lactobacilli* up-regulate mucin formation and simultaneously slow its breakdown, thus enhancing barrier function [10] and mostly via the production of postbiotics such as butyric acid [11]. They tend, therefore, to be fence-builders.

Gram positive and negative species both produce proteolytic enzymes, but the best-known probiotic species (i.e. the gram positive *Lactobacilli* and *Bifidobacteria*) prefer prebiotic fibers as fuel so tend to stay in the lumen of the colon where these fibers arrive. Bacteria which prefer protein migrate towards mucins and the colon wall; and if they are coated with LPS, or produce pro-inflammatory polysaccharides, they are likely to trigger substantial inflammatory stress in the mucosa. These bacteria therefore tend to be fence-breakers.

Not all of them, however, are detrimental to health. Paradoxically, the gram-negative mucolytic species Akkermansia muciniphila is associated with anti-inflammatory, anti-obesity, metabolic and immunological benefits [12] and is generally considered to be probiotic [13]. Nor are all gram-positive species exonerated [14]. *Ruminococcus torques* is a gram-positive bacterium which not only degrades mucin but also encourages the growth of other mucinolytic species, and is linked to increased risk of IBD [14,15].

Akkermansia and aside, a general excess of gram-negative proteolytic species that, due to dietary shift, are no longer being kept in check by saccharolytic prebiotic species [16], is linked to mucosal thinning and an increased incidence of IBS and IBD [5,17]. Over the same time period, however, while IBS and IBD were increasing (together with many other NCD's), the frequency of peptic ulcers fell [18]. How might this be explained?

If the mucous layer is indeed monitored, mucosal thinning in the colon should lead to a physiological response involving increased mucin synthesis by goblet cells, and perhaps reduced secretion of mucin-destroying proteases by Paneth cells [19,20]. This might only

occur locally or it could be a systemic process whereby mucous thinning in the colon leads, via vagal coordination [21], to mucous growth and therefore reduced ulcerogenesis - in more proximal parts of the GI tract.

The reduced risk of peptic ulcers is, to date, the only health benefit I have heard of that might plausibly be linked to the modern diet. And now let's turn back to the fences that exist between us and the rest of the world, and consider the old friends hypothesis.

A recent post [22] cited the wonderful Polly Metzinger, whose re-imagining of the immune system as a harm detector rather than a self/non-self-discriminating system helped create a deeper appreciation of immune function and malfunction. Graham Rook is another profound thinker, who in 2003 proposed that the hygiene hypothesis [23] be replaced by the old friends hypothesis [24].

The hygiene hypothesis suggests that the recent increases in allergy and autoimmune disease are caused by living in excessively clean environments. The immune systems of children growing up in modern homes are being insufficiently challenged, leading to imbalance, malfunction and the acquisition of inappropriate targets.

Nature abhors a vacuum, however and microbes teem in the most sterile of homes. According to old friends it is only a certain sub-set of microbes that we miss, non-pathogenic species we co-evolved with and which train our immune systems.

(Old friends were at some point in time new ones, and perhaps not friends at all; they may have been foes before eventually evolving into commensals, paralleling the development of mitochondria and chloroplasts).

Non-pathogenic yeasts supply the 1-3, 1-6 beta glucans that our immune cells recognize and benefit from [25] and non-pathogenic bacteria are just as important. Commensal bacterial species that occur widely in the world around us, and on and in our bodies, are an important part of our innate immune system and play a central role in defending us from infections [26].

There is also evidence that they positively modulate or train our immune systems, as the yeasts do, and that their removal from our increasingly urbanized environment has made us more vulnerable to allergy and autoimmunity [27].

Some of the most interesting examples occur in the gram-positive *Mycolicibacterium* genus.

Mycolicibacterium fortuitum and *neoaurum* are occasional pathogens [28], but *M. aurum Aogashima, M. kyogaense* and *M. obuense* are categorized as commensals. So safe that cooked cultures of *M. aurum Aogashima* are being considered as food additives [29,30], these microbes occur widely in soil and water. We therefore used to encounter them very frequently, and still do albeit in much diminished numbers [31].

Neither fence-breakers nor builders in the context of the gut, these commensals help maintain fences elsewhere, for example in the central nervous system, as they pass through us. Old friends with benefits, the *Mycolicibacteria* have been shown to exert potent immuno-modulatory [32,33] and linked anti-inflammatory effects [34]; a dual effect which reduces central neuroinflammation [35].

Reducing neuroinflammation protects and restores the blood/brain barrier [36,37], another fence which must be maintained if we are to be our true selves.

There is rather good evidence that neuroinflammation alters neuroplasticity in the limbic system, making this emotion-coding neuro-circuitry more excitable and driving us towards anxiety and depression [38], and to anger [39]. There is good evidence also that an exaggerated inflammatory stress response makes people vulnerable to stress-related disorders [40-42].

It is therefore plausible that the removal of anti-inflammatory nutrients and prebiotic fibers from the modern diet has contributed to the ever-increasing frequency of anxiety and depression [42-45] and the stress-related diseases; and that the progressive banning of old friends from our near environment [31] has also been involved.

This is supported by recent findings of *Mycolicibacteria's* ability to damp neuro-inflammation while at the same time providing anxiolysis [34,47-49,51], to modify the activity of immuno-responsive neurons in the limbic circuit [50] and to reduce various physiological signs of chronic stress [51].

Given progressive urbanization (since 2008, the majority of the world's population has lived in towns and cities), and our gradual retreat from carbon-based nature into silico [52], one has to wonder whether the effective removal of *Mycolicibacteria* from polite society has contributed to today's culture of depression and anxiety.

The intensive marketing of psychotropic drugs plays into this culture [53], as has dietary shift. This explains the therapeutic effects of pharmaconutritional interventions (omega 3 PUFA's, polyphenols, prebiotics and saffron), but one should not under-estimate the impact of the natural world; it has long been known that exposure to nature can be an effective treatment for depression and anxiety [54].

Studies have shown that this kind of exposure reduces stress [55], with associated positive changes in brain function [56]. Other researchers have raised the possibility of immuno-modulation via exposure to natural volatiles and microorganisms [57] and this, together with the proven anxiolytic and anti-depressant effects of forest bathing [58] and therapeutic horticulture [59], raises the possibility of bringing a healing forest to Dunsinane.

Providing that the forest bears *Mycolicibacteria*.

The blood/brain barrier is, of course, a local section of the larger active physiological barrier of the vascular endothelium, the health of which impacts all organs and tissues. It has recently been discovered that vascular endothelial structure and function is influenced by microbial components such as the yeast-derived 1-3, 1-6 beta glucans, which apparently play a critical role in encouraging angiogenesis [60,61]. Here is another example of the importance of commensals in maintaining good fences.

We could re-introduce many commensals into our diet by consuming friable tilth, which sounds delicious but means not cleaning our foods so aggressively. Leaving specks of dirt on fruits and vegetables would increase our intakes of i.e. *Mycolicibacteria*, but in these times of agrochemical warfare it could also expose us to higher levels of biocides. Instead of eating a peck of dirt, a standardized *M. aureum* supplement or food additive offers a safer and more consistent alternative.

One such is immy [62].

There is a cancer connection. With a fair amount of data indicating that the *Mycolicibacteria* exert immunomodulatory effects that might reduce cancer risk [63-68], a clinical Phase 2 study in pancreatic cancer showed promise [69], although an earlier Phase 3 lung cancer trial had been less convincing [70].

But there is a more to microbial life than *Mycolicibacteria, Lactobacilli* and yeasts.

There are the Candidate phyla radiation (CPR) bacteria, a very recently discovered universe of microbes which may account for an astonishing 50% of all bacterial life [71]. They are in the human microbiome [72], drinking water [73], soil [74] and everywhere else besides, and they too are symbionts. Their importance to our health is unknown, but they are probably training our immune systems too, likely (as do the yeasts) via M-cells.

In the final analysis our immune, central and vascular systems (and therefore all our other systems) interact constantly with nature, of which we are a part. We may be bound and defined by fences, but we are not islands and nor should we seek to be. It is time to welcome old friends back into the folds and the creases of our lives.

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Volume 19 Issue 5 May 2024