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Persisting consequences of intestinal infection.
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PERSISTING CONSEQUENCE OF INTESTINAL INFECTION: SUMMARY OF THE SEMINAR

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INTRODUCTION

Infectious diarrhoea is a global public health problem with high mortality and morbidity, particularly among children of the developing world. Each year, approximately 750,000 children under five years old die from severe, dehydrating diarrhoea and dysentery worldwide, and millions more are hospitalized, mostly in low-resource countries (*Liu* et al., 2012). In addition, many more children suffer from diarrheal disease-associated malnutrition and its adverse consequences on physical and cognitive development, which perpetuates the cycle of poverty.

While the brunt of the morbidity and mortality burden due to these infections are in the developing world, acute infectious diarrhoea is also a frequent cause for outpatient visits and hospitalization throughout the developed world and is a significant health problem. For example, Scallan and colleagues published recently updated estimates for foodborne illness in the United States (*Scallan* et al., 2011a, 2011b). Based on empirical modelling of active, passive and outbreak surveillance data it was estimated that each year 31 major pathogens acquired in the United States caused 9.4 million episodes of diarrhoeal illness, 55,961 hospitalizations, and 1,351 deaths. In addition, it is estimated that unspecified agents, resulting in 71,878 hospitalizations and 1,686 deaths, caused approximately 38.4 million episodes of domestically acquired foodborne illnesses.

While the acute consequences would appear to be of global significance and drive science and public health efforts to mitigate the problem, there is growing evidence linking such infections with a myriad of chronic health consequences including neurological, haematological and rheumatological systems (*Lindsay*, 1997). The accounting of these chronic health consequences beyond that of acute disease needs to be understood and considered in the global burden of disease assessment to inform policy and decision making around food safety and sanitation policy globally, and emphasize the reduction of enteric infection among those at high risk (e.g. travellers' and deployed military and children living in resource-poor environments) through primary and possibly secondary prevention strategies.

The difficulty of understanding how such infections may cause chronic health problems cannot be overstated, given the range of pathogens (viruses, bacteria, parasites), the genetic and acquired host factors, the often repeated infections in a person's life, and the interactions between complex neuroendocrine, immunological, and microbiological systems, many which are not well understood. But what is clear is that acute infections can colonize, invade and exert their effects locally and systemically at the individual level and chronic pathological changes to these organ systems have been noted. Thus,

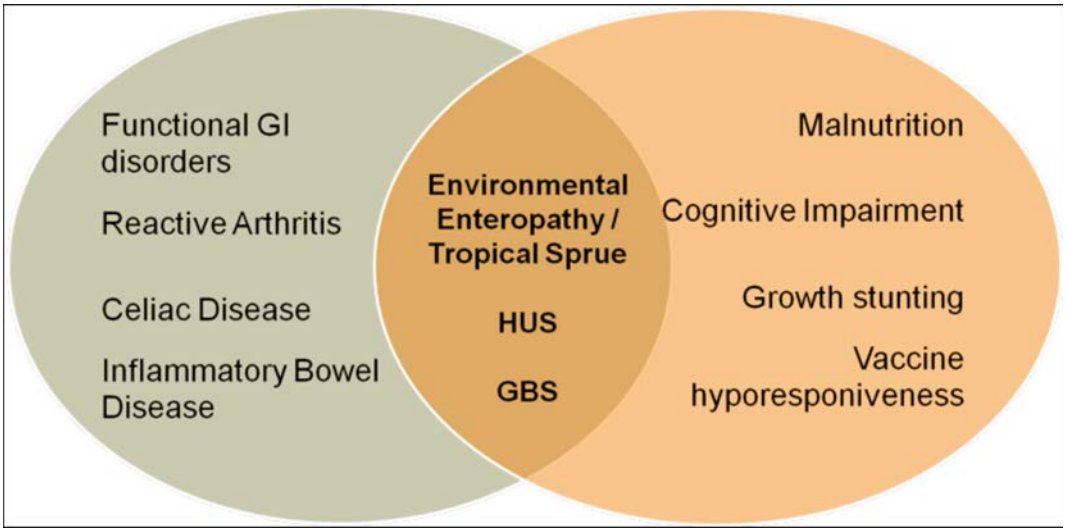

Figure 1: Persisting consequences of intestinal infection in developing (oval on right) and/or developed world (oval on left).
GI – gastrointestinal; HUS – haemolytic uremic syndrome; GBS – Guillain Barré Syndrome.

the aim of this conference was to assess our position in terms of epidemiological and pathological-aetiological understanding of the phenomenon, identify gaps in knowledge, and describe future directions related to the challenge of persisting consequences of intestinal infection.

EPIDEMIOLOGY: DEFINING THE PROBLEM

Epidemiological research is fundamental and complementary to our understanding of disease and development of primary, secondary and tertiary interventions. To put the current evidence in context, epidemiological research can identify knowledge gaps and define research priorities for increasing understanding in the areas of disease attribution, burden of disease, clinical characterization and management. A number of frameworks designed to elucidate the epidemiologic determination of causation have been advanced over the years (*Parascandola*, 2011). Koch's original postulates proved effective at establishing disease-pathogen relationships but fall short with more complex associations (*Evans*, 1976; *Marshall* et al., 1985). In recent years, Bradford Hill's criteria have been more commonly used to describe complex relationships and their epidemiology (*Bird*, 2011). Hill's criteria include strength of association, consistency of effect, specificity of effect, temporality, biological gradient or dose response, and biological plausibility to form the basis of an argument for causation and have been used successfully to establish the pathogenic role of *H. pylori*, HIV and toxins (*Szklo* and *Nieto*, 2007).

Emerging from the literature is an understanding that there are persistent consequences which are both common and unique to populations when stratified by geo-economic strata. In Figure 1 the overlapping ovals shows those issues that are primarily problems of the developed world (oval on left), while individuals in resource-poor settings suffer more from the problems

shown on the right. In the overlapping area is shown those problems currently understood to be more common to both populations. While such a divide is convenient and may be due to differences such as genetics, diet, and other unique environmental influences, it may also artificially de-emphasize possible similar pathogenic mechanisms and disease processes which may have different manifestations in a different human-environmental setting. Be that as it may, there is an emergence of evidence which describes disparate persisting consequences of acute enteric infections among those who have access to clean food water and sanitation, and those who do not.

POST-INFECTIOUS CONSEQUENCES: A DEVELOPED WORLD PERSPECTIVE

Despite food safety regulations, public education and advanced agricultural systems, occurrence of foodborne illness and other enteric infections in the developed world are not infrequent. In this seminar, Porter and colleagues (page 41) describe the utilization, challenges and opportunities of the US Department of Defense (DoD) medical encounter databases and serum repository in understanding of the problem of chronic consequences of enteric diseases. Historically, well-designed epidemiologic studies have been at the fore of linking exposures with outcomes and have enabled estimates of outcome risk, identification of host- and pathogen-specific risk factors, and understanding the timing from exposure to outcome. Studies of the post-infectious sequelae of enteric diseases are no different as highlighted by several systematic reviews on the epidemiologic evidence where functional gastrointestinal disorders appear to be most substantiated in addition to reactive arthritis (*Halvorson* et al., 2006; *Thabane* et al., 2007; *Deising* et al., 2013; *Pike* et al., 2013; *Poropatich* et al., 2010; *Porter* et al., 2013).

While these studies have enhanced our appreciation of the acute/chronic disease link, they have certain limitations. Epidemiological studies do poorly in informing disease mechanisms, are fraught with challenges in controlling for unmeasured factors and generally are only able to account for a fraction of explainable risk (though there are notable exceptions where the attributable fraction is stronger such as in the case of some strains of *Campylobacter* associated with GBS), and misclassification of both exposures and outcomes generally will bias associative estimates towards the null. Relatively rare events are also harder to study in rigorous cohort study designs without large and expensive studies. Despite these limitations, continued epidemiological studies from a diversity of populations and designs are needed to validate initial findings as well as explore new associations between acute enteric infections and the growing spectrum of illnesses.

An example of one such chronic health illness, coeliac disease, is an illustrative example of the complexity in which the immune system, the environment, and infection may interact to cause disease. In this seminar Murray (page 71) describes some unique observations on the pathogenesis and triggers of coeliac disease (CD), an increasingly common chronic disease affecting primarily the upper small intestine associated with significant morbidity and mortality in much of the developed world. While there is certainly a genetic predisposition to coeliac disease which is required, not everyone

with this predisposition will develop disease, and the onset of coeliac disease can occur at any time in someone's life suggesting an environmental triggering event. It appears that infection-colonization events in early life may have an impact on risk given the findings of higher risk of CD in individuals born via caesarean section (*Decker* et al., 2010; *Marild* et al., 2012), and weaning in the winter months (*Ivarsson* et al., 2003). These events can alter the nature of the microbiota. It has been clearly shown that microbiota are important for immunological maturation of the host (*Lanning* and *Knight*, 2005; *Sjogren* et al., 2009; *Chung* et al., 2012), but how the early constitution of an individual's microbiota can have affects such as susceptibility to the loss of tolerance a grain protein remains a mystery and opportunity to study.

Emerging evidence is also suggesting that CD may be triggered after an acute enteric infection in some individuals. Anecdotal reports and case series suggesting an association have been described (*Landzberg* and *Connor*, 2005; *Ginsburg* and *Bayless*, 2008; *Chae* et al., 2010). It has also been described that exposure to three or more infectious gastroenteritis events in young children at or around the time of introduction of follow-on formula was associated with a substantial increased risk of childhood diagnosis of coeliac disease (*Falth-Magnusson* et al., 1996). More recently, a case of a healthy subject who developed sudden irritable bowel syndrome (IBS)-like symptoms after a confirmed episode of *Campylobacter jejuni* enteritis was subsequently diagnosed with new onset CD (*Verdu* et al., 2007). Studies among the previously described DoD medical encounter system database have also recently been reported which support association between bacterial acute enteric infection (in particular *Campylobacter*) and the onset of CD. (*Riddle* et al., 2012). One explanatory hypothesis which needs to be confirmed is that *Campylobacter jejuni*, which has been shown experimentally to permit the translocation of normal non-invasive microflora (*Chen* et al., 2006; *Kalischuk* et al., 2009; *Kalischuk* and *Buret*, 2010), could trigger aberrant immune responses/loss of tolerance to co-transported luminal antigens, including gluten peptides, across the intestinal barrier. In certain susceptible individuals primed towards a mucosal immune response towards such antigens this could result in loss of tolerance to these antigens due to an inappropriate inflammatory response (*Jabri* et al., 2005; *Jabri* and *Sollid*, 2009). As demonstrated in animal models of gluten sensitivity (*Verdu* et al., 2008; *Natividad* et al., 2009), gastrointestinal infection may trigger or facilitate the onset of clinical CD, either by increasing intestinal permeability or enhancing uptake and dysfunctional anti-gliadin immune response in the genetically susceptible host (*DeMeo* et al., 2002; *Fasano* and *Shea-Donohue*, 2005).

POST-INFECTIOUS CONSEQUENCES: A DEVELOPING WORLD PERSPECTIVE

Human enteric infection in the developing world is different from that of the developed world on a number of features including the age of onset of infection (earlier), force of infection (multiple repeated exposures), variety of pathogens (more diverse), nutritional status of the host, as well as a number of other factors including co-infection, diet and genetics. As such, approaching

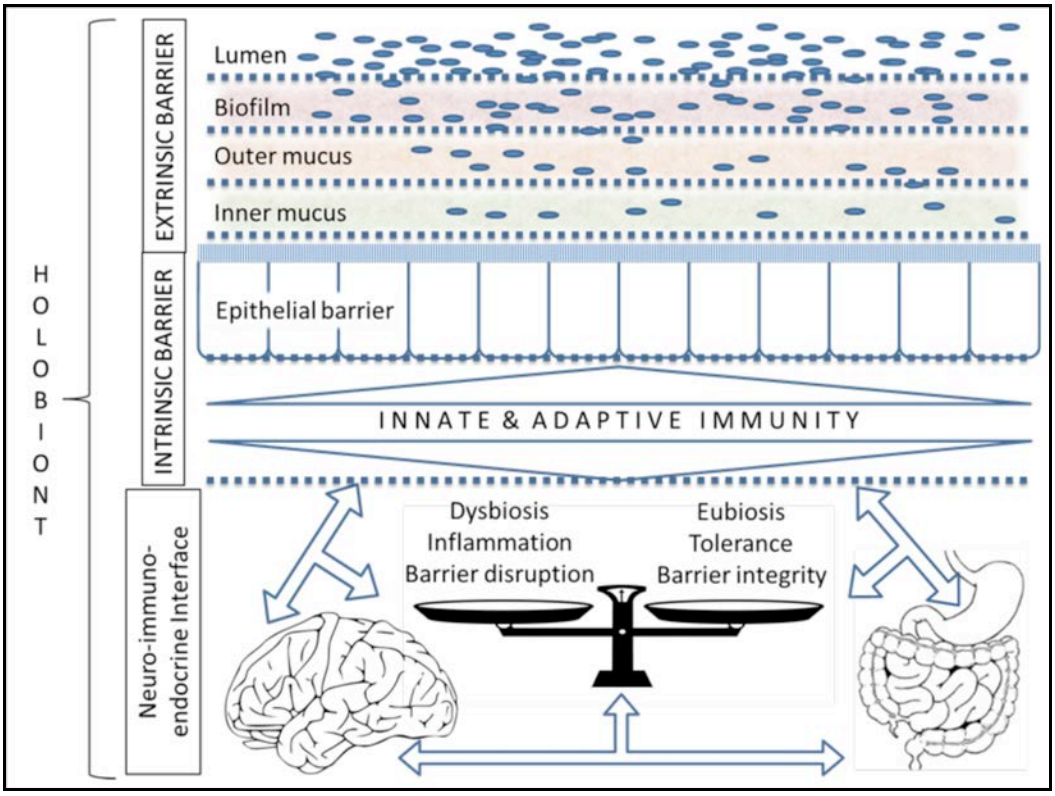

Figure 2. Framework to understand the patho-aetiology of persisting consequences of acute enteric infections.

an understanding of the link between infections and chronic illnesses in this population is challenged as the "one-infection" leads to "one outcome" approach is difficult to tease out. A unique study entitled the "Malnutrition and Enteric Infections network" ("MAL-ED") exploring the aetiology, risk factors and interactions of enteric infections on child health was presented with a unique design constructed for this environment (Malnutrition & Enteric Infections Network MAL-ED: The Interactions of Malnutrition & Enteric Infections: Consequences for Child Health and Development. Project website (accessed Dec 10, 2013) http://mal-ed.fnih.org/). While results presented were preliminary and did not include cognitive and nutritional metrics, the results are shedding light on new insights on the often described "vicious cycle" of enteric infections leading to enteropathy leading to malnutrition and effects on growth, cognition and immunity, which themselves contribute to increased susceptibility to enteric infections (*Guerrant* et al., 2008; *Moore* et al., 2010). The results presented by McCormick and colleagues (page 23) expand on this conceptual model but also challenge our understanding of the significance of the repeated asymptomatic episodes of infections with disease-causing potential on growth and nutrition outcomes. It would appear that infection with pathogens which may or may not be associated with symptoms is the driving factor for the chronic consequences in these populations.

Expanding on the findings of MAL-ED, Petri and colleagues (page 61) described how recurrent infections, and in particular some combinations of protozoal and bacterial infections, can result in a subclinical condition of environmental enteropathy (EE) characterized by disruption of intestinal architecture and chronic inflammation. Such changes would appear to have direct effects on nutrition, the individual's ability to respond to additional infections, and evidence also suggests that such a condition may negate the valuable contributions of some orally-administered vaccines through evidence of hyporesponsiveness (see: Old Herborn University Seminar Monograph 24; Development of strategies to overcome barriers to effective mucosal immunization of infants in developing countries).

PATHOGENIC MECHANISMS: A GROWING FRAMEWORK OF COMPLEXITY

While epidemiological studies are increasing our confidence that there are real associations between enteric infections and chronic health effects, these data are limiting and only tell us that there is a problem and, given the magnitude, ought to do something about it. It is critical is to understand what is occurring in order to explain these observed associations. Based on presentations and discussions at this Old Herborn University Seminar, a framework has emerged by which to understand the problem (Figure 2). At the gut surface there is an increasing density and complexity gradient of microbial flora (both bacteria and viruses) that are found in the lumen of the GI tract in the oral to aboral direction. Within the lumen are also nutrients (taken in by the individual and produced by the flora), chemicals, antibiotics and non-digestible matter which shape and contribute in part to the diversity of this microbial milieu. There is also a microbiome gradient which exists from the lumen to the surface of the enterocyte where there is a decreasing density as you get closer to the cell surface. It is within this interface, often referred to as the extrinsic barrier which acts as a two-way filter, where many important processes take place including allowing nutrients to be absorbed and keeping harmful bacteria at bay. Underlying this extrinsic barrier is what is often referred to as the intrinsic barrier which is made up of a layer of host cells. While the figure is a simplification, this layer is not homogenous and includes a number of cell types which are derived from stem cells and include absorptive enterocytes, mucus-secreting goblet cells, entero-endocrine cells and Paneth cells. This cell layer is highly dynamic and includes complete turnover every few days and relies on a delicate balance between cell proliferation and cell death. This cell layer has a diverse set of functions which include production of antibacterial peptides, sampling of luminal contents, and absorbing important nutrients and fluid into the host circulatory system. This layer is at an interface between the luminal extrinsic barrier and the host innate and adaptive immune system which largely takes in the sub-epithelial level where neuro-endocrine, circulatory and cellular and humoral immune cells systems interface. While the basic systems involved are delineated in such simple terms, each of these systems are complex, and it is likely that it is the interaction of each of these systems which needs to be understood - like a puzzle which is made up of hundreds of other puzzles.

Several presenters revealed insight

into pathogenic mechanisms which have advanced our understanding of a piece of the puzzle. Buret and colleagues (page 87) reported on recent findings from an animal model suggesting that enteropathogen-induced disruptions of the commensal microbiota have a part play in triggering the sequence of events that result in various intestinal and extra-intestinal chronic health outcomes. Data from animal models of campylobacteriosis and giardiasis suggest that infection by enteric pathogens may promote the transcellular and paracellular translocation of non-invasive commensal bacteria, as well as disruptions of the composition and structure of microbiota biofilms. Such actions then lead to the activation of the host autoimmune reactions that are implicated in the production of post-infectious complications. Beyond the well-established need to better understand host-pathogen cross-talks, as well as interactions between the host and its microbiota, these observations lay the foundations for future research into enteropathogen-microbiota interactions and highlight that the mechanism of intestinal dysbiosis (a process whereby an enteric pathogen disrupts the normal commensal flora such that an imbalance among microbial populations occur on a body surface, often with deleterious effects on health) is a central piece of the puzzle to solve. The availability of animal models like these is quite useful to help better understand gut homeostasis.

Building on this theme (and adding an additional layer of complexity), Collins (page 107) describes the phenomenon of acute enteric infections and functional gastrointestinal disorders as an important model to understand the relationship between the gut-brain axis, the microbiome and acute infection. In simple terms, infection, stress and antibiotics (alone or in combination) can have a disrupting effect on the balance within the gut epithelial barrier and microbiome. This disturbance in susceptible individuals can result in abnormal immune activation which may further alter the balance of the microbiome in the gut (dysbiosis). This dysbiosis may have direct effects on the neuroendocrine system with central effects on the brain (perception/pain), as well as local effects on the enteric system (e.g. motility). While studies have shown that risk for functional disorders are associated with psychiatric co-morbidities, the opposite has been described in animal models where microbiome changes can change behaviour and brain neurochemistry (*Bercik* et al., 2011). Finally, it must not be forgotten that stress itself can have an impact on the gut epithelial barrier and increase risk of infections including enteric infections, which in combination with stress appear to increase the risk of functional disorders (*Lyte* et al., 2011; *O'Malley* et al., 2011). Thus, in our framework of understanding, it is important to consider the impact of the important two way cross-talk between the brain and the gut (see: Old Herborn University Seminar Monograph 26; The gut microbiome and the nervous system), and how these interact with the microbiome to result in dysbiosis and disease associated with nervous system disturbances.

Finally, Chang and colleagues (page 13) described evidence from a *Campylobacter* model in rats whereby infection, potentially through molecular mimicry, can have an effect on gastric motility, which in itself may lead to a type of dysbiosis where the GI system's ability to maintain healthy levels of bacteria in the small intestine can be disrupted. The findings of this model suggest that there may be multiple mechanisms by where a single pathogen my cause a chronic health consequence.

THE FUTURE: UNDERSTANDING COMPLEXITY AND EXPLORING NEW FRONTIERS

As described, each of the systems that may influence the determination of persistent infectious consequences is independently complex, and together the complexity is compounded. Clearly, better tools and model systems are needed to piece together the puzzles. One such tool which may have potential is in the area of intestinal stem cell research described by van der Flier and colleagues (page 1). The stem cell intestinal epithelium model represents a unique opportunity to study adult stem cell biology and lineage specification. The combination of a rapid self-renewing tissue, evident compartmentalization of proliferating and differentiated cell types and a relatively simple, repetitive tissue architecture, is ideal for the visualization and identification of stem cell types, cell fate specification and cellular behaviour. In the past, genetic studies in mice have created a wealth of new insights on the biology of the intestinal epithelium. The recently established long term culture conditions of intestinal epithelium, especially mini-organs from human origin, may boost the research field for the next generation by providing a variety of possibilities for research and therapeutic applications of intestinal biology. The system in its current construct lacks the enteric neuroendocrine and microbiome integration, but additions of such components may be feasible and add to the utility.

New data challenge the way we understand the relationship between infection and illness. It is apparent that even though one can recover a pathogen from an individual it is often noted that that pathogen is not causing illness, which begs the question of is it a pathogen? Clearly understanding how asymptomatic infections with pathogenic organisms affect the holobiome is an important gap. In addition, with the increasing number of chronic health problems in which epidemiological associations are being found, we are challenged by understanding how big the problem is or may well be. Microbiome changes are now being associated with obesity and liver disease in developed world populations (*Henao-Mejia* et al., 2013; *Karlsson* et al., 2013; *Zhao*, 2013). Natural questions which follow include what are the factors behind these changes and could infection be one of them? Epidemiological studies and perhaps animal models could be directed at looking for such associations. A study of certain value would be to conduct a developed world post-infectious microbiome cohort studies among populations at high risk for acute enteric infection (e.g. travellers). Evaluating baseline microbiome as well as changes that may occur with travel, travel-related infections and antibiotics, and the persistence of such changes which may be linked to well defined post-infectious functional gastrointestinal disorders may offer new insights.

Finally, we need a framework which approaches the problem not only by considering the contributions of pathogens, or the host or the commensal flora, but rather as an integrated system. The concept and importance of the holobiont has emerged over the last two decades. Bacterial cells outnumber human cells by a factor of 10 to 1, and the collective genes of these bacteria outnumber our genes by 150 to 1 (*Qin* et al., 2010). We know that these bacteria are critical to our survival and include important functions such as food break down, biotransformation of nutrients, development and function of a

Box 1: Remaining gaps in our understanding and questions for future directions.

- How does the viriome interact and what of the effects of viral enteric infection on the viriome and bacteriome and vice versa?
- How do antibiotic challenges to the system interact?
- What is the relationship of enteropathy with nutrition? Can complex nutrient effects be isolated and rebalanced through nutrition?
- What is the impact of environmental chemicals on the microbiome and host factors associated with disease?
- How do neuro-immune interactions work?
- What is the nature of inflammation in various disease models? Why is inflammation sometimes healthful and sometimes deleterious?
- How do we facilitate inflammation resolution (not stopping, but helping resolution)?
- What could generational/adoptive studies teach us about the association between acute enteric infection and chronic health consequences?
- What are the short-term opportunities to treat these diseases? For example what role might faecal microbiota transplant play? Could well-characterized synthetic faecal microbiome products be useful? What might the value of microbiome feeding and topical anti-inflammatories be?
- Can continued epidemiological studies from a diversity of populations and designs validate initial findings as well as explore new associations between acute enteric infections and the growing spectrum of illnesses?
- How does *Campylobacter jejuni* trigger aberrant immune responses/loss of tolerance to co-transported luminal antigens across the intestinal barrier?
- How does the early constitution of an individual's microbiota have affects such as susceptibility to the loss of tolerance a grain protein?
- How do enteropathogen-microbiota interactions trigger intestinal dysbiosis (a process whereby an enteric pathogen disrupts the normal commensal flora such that an imbalance among microbial populations occur on a body surface, often with deleterious effects on health)?
- Could microbial toxins from enteric pathogens like ETEC and *Campylobacter* contribute to microbiome disruption and its consequent effects?

normal immune system, angiogenesis, and regulation of fat accumulation (*Singh* et al., 2013). In addition to these functions, the microbiota compete for space with pathogens and can exert other local effects to protect the host from infections. The microbiota is also adaptable which provides an advantage to the host which may need to rely on the flexibility of the microbiota structure to adapt to changes of diet or climate or infection. Bosch and colleagues (page 113) describe an elegant system in Hydra, where the microbiota is a complex and multifunctional ecosystem that is essential to the development, protection, and overall health of its host. Furthermore the dynamic relationship between symbiotic microorganisms and environmental conditions results in the selection of the most advantageous holobiont. Systems like these may provide tools to further study and explore and potentially lead to insights to prevent the unintended consequences of holobiome disturbances.

CONCEPTS AND QUESTIONS FOR FURTHER CONSIDERATION

Continued epidemiological studies from a diversity of populations and designs are needed to validate initial findings as well as explore new associations between acute enteric infections and the growing spectrum of illnesses. Studies are also needed to better understand the mechanism by which an enteropathogen such as *Campylobacter jejuni* which induces disruptions of the commensal microbiota can affect the sequence of events that result in various intestinal and extra-intestinal chronic health outcomes. Future research into enteropathogen-microbiota interactions should highlight dysbiosis as a central piece of the puzzle to solve. There may be multiple mechanisms by which a single pathogen my cause a chronic health consequence. Understanding how asymptomatic infection with pathogenic organisms affects the holobiome is an important gap. How does the viriome interact and what of the effects of viral enteric infection on the viriome and bacteriome and vice versa? Non-infectious events can also contribute to the problem of dysbiosis, as stress and antibiotics (alone or in combination) can have a disrupting effect on the balance within the gut epithelial barrier and microbiome

Clearly better tools and model systems are needed to help piece together the puzzles with which we are confronted (Box 1). Although these questions are challenging, the benefits to human life which can be achieved make the undertaking well worth the effort.

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