

July 2017

### Highlights from the 50<sup>th</sup> Annual ESPGHAN Meeting, May 2017

- Dr. John Cryan (Ireland) describes how the state-of-the-gut can affect our state-of-mind. See what's new regarding the gut-brain axis. (p. 2)
- Is the increasing incidence of childhood allergies a 'canary in the coal mine' for harmful dietary and environmental changes? (p. 3)
- Human milk is considered the gold standard for feeding infants up to age 6 months. What have researchers newly discovered about functional ingredients of human milk? (p. 4)
- Explore the next frontier of pediatric nutrition in a review of roles for human milk oligosaccharides, prominent components of human milk. (p. 5)
- Why is life-threatening necrotizing enterocolitis (NEC) more likely to affect prematurely-born infants than full-term infants? Surprisingly, the link between prematurity and NEC is a transmembrane protein called the toll-like receptor. (p. 6)
- Dietary carotenoids play a crucial role in development of vision and cognition. The carotenoid lutein has antioxidant, anti-inflammatory, and neuroprotective effects. (p. 7)

# PEDIATRIC NUTRITION NEWS



The 50<sup>th</sup> Annual Meeting of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) was held in Prague, Czech Republic 10-13 May, 2017. With the charming World Heritage city of Prague as its centerpiece, the Czech state has a history spanning more than 1,000 years.

**Prof. Ranaan Shamir (Israel)**, current president of ESPGHAN, welcomed attendees and noted that response to the 2017 ESPGHAN program was record-breaking; 4,668 participants represented 96 countries, more than 800 poster presentations reported new research findings, and 20 special interest groups met over the course of 4 days.

Dr. Shamir opened, "Just like the splendid stone bridge that connects both banks of the river Vltava in Prague, the 50th ESPGHAN Annual Meeting is an ideal platform for participants to connect and to network."

*Pediatric Nutrition News* is an educational service of Abbott Nutrition; each newsletter aims to update healthcare professionals around the world about the latest nutrition research and therapy, as reported from recent conferences.

This issue of the newsletter covers compelling questions raised in the ESPGHAN 2017 Meeting:

- Does the gut-brain axis influence normal brain development, risk for autism, or occurrence of depression?
- Why has the prevalence of childhood allergies increased in the past decade?
- What are human milk oligosaccharides (HMOs), and how are they involved in infant health?
- How and why does the infant gut become colonized with bacteria in the first year of life?
- Why are infants who are born prematurely particularly susceptible to necrotizing enterocolitis (NEC)?

# THE GUT TALKS TO THE BRAIN

## THE GUT-BRAIN CONNECTION IN EARLY LIFE

“The state-of-the-gut can markedly affect our state-of-mind,” remarked **Dr. John Cryan (Ireland)** in his Gastroenterology Keynote Lecture for ESPGHAN 2017. In fact, the gut is now recognized for its crosstalk with the brain during infant development and far beyond. Such ‘talk’ is evidenced by correlational studies in a wide range of disorders—neurodevelopmental conditions, autism, depression, anxiety, irritable bowel syndrome, and obesity.<sup>1, 2</sup> Both animal and human studies back the concept of communication between the gut and the brain.<sup>1</sup>

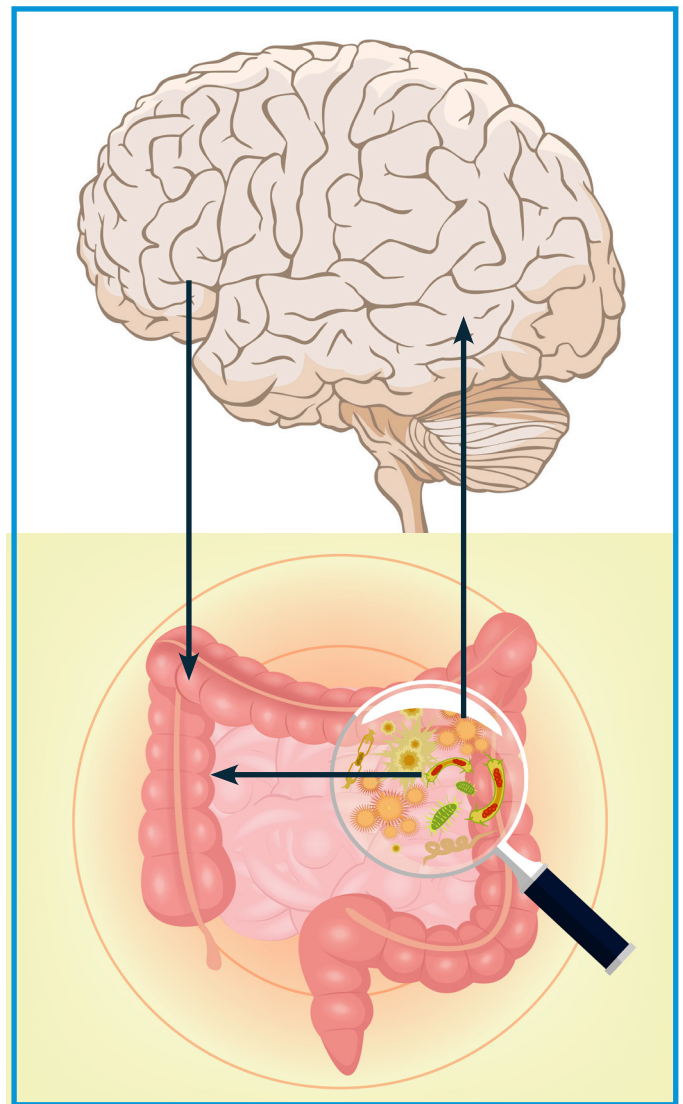
Development of the brain begins in the 3rd week of gestation and continues through infancy, childhood, and adolescence. Especially in the first years of life, the brain’s neuronal circuits grow and are rapidly remodeled by nutrition, visual and physical stimulation, and other positive learning experiences. Such growth and remodeling can also be negatively affected by aberrant stimuli like sickness, stress, and poor diet. Intriguingly, recent studies of gut-brain communication suggest that commensal microbes living in the gut are likely to be involved in the conversation too.

## THE GUT MICROBES ENTER THE CONVERSATION

Researchers have discovered that gut microbes are capable of producing most neurotransmitters found in the human brain.<sup>2</sup> The brain-gut-microbiota axis is a bidirectional communication system that enables gut microbes to communicate with the brain and the brain with the gut.<sup>2</sup>

Growing evidence makes it increasingly clear that gut microbes can influence central neurochemistry and behavior. Specifically, studies show that certain bacteria have an impact on stress responses and cognitive functioning.<sup>2</sup> Early findings suggest that bacteria signal the brain by way of the vagus nerve.<sup>3-6</sup>

Postnatal neurodevelopment and gut colonization occur in parallel.<sup>7</sup> That is, during the first year of life when the brain is growing and changing most dramatically, the gut is also getting colonized by



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microbes. In fact, animal studies have shown that early life stress is associated with alterations in the gut microbiota.<sup>8, 9</sup> Yet another animal study showed that antibiotic-induced microbial imbalance in the gut could impair object recognition, a measure of cognition.<sup>10</sup>

Irritable bowel syndrome is regarded as the prototypic disorder of the brain-gut-microbiota axis that can respond to probiotic therapy.<sup>2</sup> Early findings associate anxiety and autism with specific alterations of the gut microbiota, but confirming studies are needed.<sup>11</sup> It is indeed exciting to envision the possibility of manipulating the gut microbiota with probiotics, prebiotics, synbiotics (prebiotics + probiotics), or even antibiotics as a way to treat gut-brain axis disorders such as depression and autism.<sup>2</sup>

# ALLERGIES AND NUTRITION

## ARE ALLERGIES THE ‘CANARY IN THE COAL MINE?’

Well into the 20<sup>th</sup> century, coal miners brought canary birds into the mines as an early-warning signal for toxic gases such as carbon monoxide. **Dr. Susan Prescott (Australia)** suggested that the dramatic increase in childhood allergies in recent years may in fact be ‘the canary in the coal mine’ for health risks in the modern environment. The immune system is highly sensitive to changes in the environment, and there are obvious links between immune dysfunction, inflammation, and certain non-communicable diseases (NCDs).<sup>12, 13</sup> Dr. Prescott specifically warned that modern dietary patterns may be a common factor in the rise in NCDs today—allergy, as well as bowel disease, diabetes, and childhood obesity.

According to Dr. Prescott, there has been a 5-fold rise in the prevalence of allergies in preschoolers over the past decade in Australia; by age one year, 25% of infants have signs of allergy, especially food allergy. Reduced gut microbial diversity, especially in the early months of life, predicts allergy/asthma development.<sup>14</sup> There is now evidence that the high-fat, low-fiber ‘Western’ diet leads to lower biodiversity of the gut microbiota, ultimately altering immune development and metabolic function.<sup>15, 16</sup> As a result, risk for allergic disease may be increased as gut barrier function is disrupted, systemic antigen load increases, and low-grade endotoxemia ensues.<sup>16</sup>

Dr. Prescott challenged, “Can we improve our microbiome?” She advised that changing our diet is the quickest way of changing our gut bacteria. She emphasized the importance of consuming more fiber, which is particularly important for pregnant women (current fiber guideline 25 g/day). The mother’s gut microbiota can influence the health and development of the fetus as well as the newborn. In the first year of life, breastfeeding is a major influence on selective establishment of gut microbial genera, notably the genus *Bifidobacterium*.<sup>17</sup> Once complementary foods are introduced, Dr. Prescott advised eating more fruits and vegetables because

non-pathogenic bacteria on their surface can help maintain microbial diversity in the gut. Fruits and vegetables also contain high levels of non-digestible complex carbohydrates called oligosaccharides and polysaccharides that promote the growth of beneficial bacteria in the gut. On the other hand, highly processed, fiber-depleted foods in a ‘Western’ diet limit the biodiversity of microbes growing in the gut.

### New book available in September 2017:

*The Secret Life of Your Microbiome: Why Nature and Biodiversity Are Essential to Health and Happiness* by Susan Prescott and Alan Logan.

Dr. Prescott concluded that a loss of microbial diversity in the environment may be leading the way to increasing prevalence of allergy and other NCDs. She warned, “Each ‘cleaner’ generation may be starting life with a smaller endowment of ancient microbes than the last. We don’t even know what we’ve lost.” This message is the theme of the new book she has co-authored with her husband Dr. Alan Logan, which will be available in the fall of 2017.



The Baroque façade of the Loreto Chapel highlights this pilgrimage site and historic monument in the Castle District of Prague.

## FUNCTIONAL COMPONENTS OF HUMAN MILK: THE GOOD, THE BAD, AND THE “BUGS”

Human milk is the gold standard and natural food for infants. Recent studies reveal insights into some functional components of milk, bringing to light the good, the bad, and the “bugs,” as discussed in an ESPGHAN 2017 session.

**The good:** The human milk fat globule membrane (MFGM) surrounds a triglyceride core of the milk fat globule, thus enabling fat to be transported in an aqueous environment.<sup>18</sup> The MFGM also contains bioactive proteins that play key roles in infection protection, e.g., lactoferrin. MFGM is present in human milk but absent from infant formula because it is discarded with cow milk fat in the formula-production process. **Dr. Niklas Timby (Sweden)** discussed new study results showing that retaining or adding MFGM to formula promises to help fill the gap between human milk and formula.<sup>19</sup> Study results showed evidence of improved cognitive performance and decreased infections in early life for infants given formula containing MFGM.<sup>19</sup> However, study numbers have been relatively small, and study designs are heterogeneous; much work remains in order to build a compelling body of scientific evidence on clinical benefits.

**The bad:** **Dr. Nicolas Olea (Spain)** reported that researchers have identified contaminants in human milk. They found high levels of persistent organochlor pollutants (POPs, from pesticides), parabens (antimicrobial preservatives from personal care products or pharmaceuticals), and ultraviolet (UV) filter chemicals from sunscreens. POPs, POPs metabolites, and polychlorinated biphenyls can be eliminated from the body by secretion in human milk.<sup>20</sup> Parabens were detected in more than half of human milk samples in a Canadian study,<sup>21</sup> and UV filters were found in 85% of milk samples in an Austrian study.<sup>22</sup> Health outcomes for infants exposed to these contaminants are not known, but such contaminants in human milk are worrisome and call for further study.

**The bugs:** **Dr. Marie Carmen Collado, (Spain)** emphasized the importance of exposure to intestinal microbes in infancy. Such exposure affects health and disease in later life through programming of immune and metabolic pathways. Dr. Collado reported that an infant’s microbial gut colonization begins *in utero* as a result of contact with maternal microbiota in the placenta and in amniotic fluid.<sup>23</sup> Researchers continue to learn about colonization via human milk and other pathways, such as contact during delivery and postpartum skin touch with breastfeeding.<sup>24, 25</sup>



The classic red Prague tram shuttles passengers through the charming streets of the city.

# HARNESSING HUMAN MILK OLIGOSACCHARIDES FOR HEALTH

Educational programs on immune development and Human Milk Oligosaccharides (HMOs) revealed new findings from this ‘next frontier’ of pediatric nutrition, as reported by renowned researchers and clinicians.

**Dr. Philip Calder (UK)**, University of Southampton, opened the program by reviewing development of the immune system in the first year of life.<sup>26</sup> *Protection and tolerance* are the principal roles of the immune system. For protection, the immune system defends its host from pathogens and also helps eliminate toxic substances that enter through mucosal surfaces lining the respiratory and intestinal tracts. At the same time, the immune system must ‘tolerate’ beneficial substances in and on the body, such as the foods eaten and commensal microbes living on the skin and in the gastrointestinal and respiratory tracts. Humans have 2 pathways for immune response—innate and acquired. In the first months of life, the infant relies largely on its innate immune pathway for general pathogen destruction. Over the course of the first year of life, an infant is exposed to specific pathogens and toxins, so the infant’s acquired immune pathway matures and produces antibodies targeted to specific harmful invaders, thereby building a memory for removal of threatening substances. The newborn infant also gets some immune protection by passive transfer of antibodies in milk from mom.

**Dr. Ardythe Morrow (USA)**, Cincinnati Children’s Hospital Medical Center, introduced human milk oligosaccharides (HMOs), which are prominent and diverse components of human milk that affect infant wellness. A clue to the functional role of oligosaccharides in human milk comes from the observation that oligosaccharides are present in milk of the echidna at levels higher than lactose, the usual nutrient and most abundant carbohydrate of milk. This observation suggests that milk of this early mammal played a role even more important than nutrition.<sup>27</sup>

HMOs are considered *functional carbohydrates* because they protect breastfed infants against infection and resultant diarrhea.<sup>28</sup> Chemically, HMOs are structurally diverse glycans, i.e., monosaccharides or amino sugars linked together in different combinations.<sup>17, 29</sup> All HMOs contain the disaccharide lactose (galactose-glucose) at their reducing end, and

the chain is elongated by the enzyme-directed addition of other saccharides.

HMOs were first recognized as a *Bifidus factor*.<sup>30</sup> This factor serves as a prebiotic, i.e., a metabolic substrate for desirable bacteria that colonize the intestine and displace harmful bacteria.<sup>29</sup> As such, HMOs could shape the intestinal microbiota of the breastfed neonate. **Dr Christina West (Sweden)** of the Umeå University noted that HMOs are now known to be more than just “food for bugs.” Many HMOs are structurally similar to carbohydrate groups linked to extracellular receptors expressed by intestinal epithelial cells. A growing body of evidence suggests that HMOs serve as soluble decoy receptors, which bind pathogens, thus preventing their attachment to infant mucosal surfaces and lowering risk for infection by these viruses or bacteria.<sup>29</sup> HMOs are otherwise involved in modulation of epithelial and immune cell responses, including

## Why does echidna milk contain oligosaccharides?

The echidna has spines like a porcupine, a beak like a bird, a pouch like a kangaroo, and is egg-laying like a reptile. The echidna evolved about 50 million years ago from an aquatic platypus-like ancestor. It lives in Australia and is one of the most primitive mammals on earth today. Nutrition scientists now recognize that oligosaccharides serve as prebiotics, supporting growth of beneficial microbes, in turn keeping harmful microbes from proliferating. In the echidna’s ancient, microbe-filled environment, the ability to defend against microbial infection was no doubt an important survival benefit.

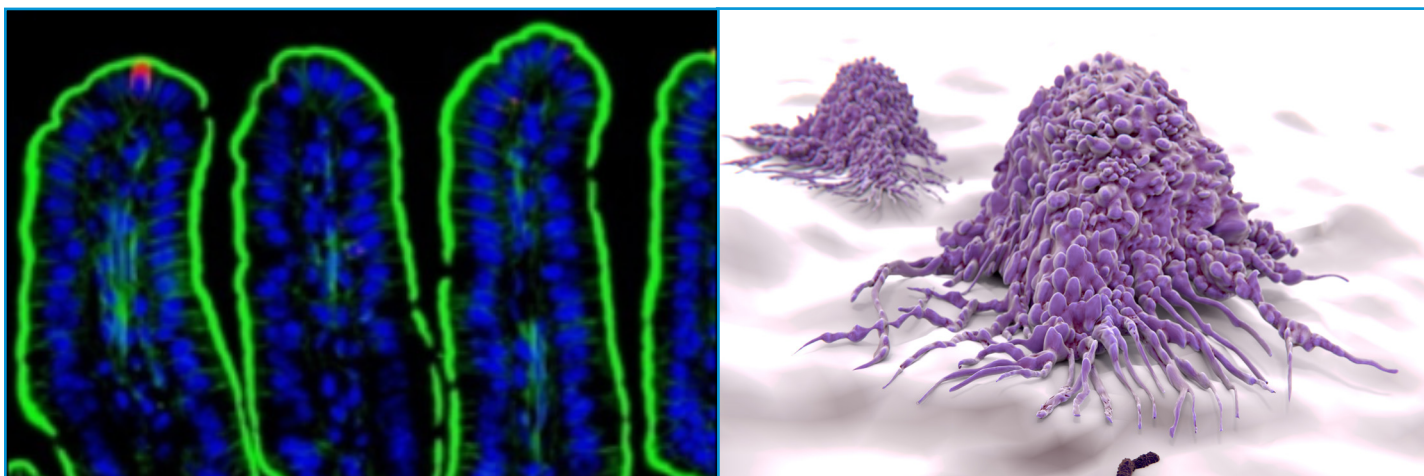


reduction of excessive mucosal leukocyte infiltration and activation.<sup>29-31</sup> To illustrate these concepts, Dr. West described a fascinating natural experiment—mothers who can and mothers who cannot make a common HMO called 2'-fucosyllactose (2'-FL). The difference is genetically controlled by the mom's ability to produce an enzyme that links a fucose sugar residue to lactose, and moms are called *secretors* and *non-secretors*, respectively. Breastfed infants of 2'-FL *secretor* mothers could much more readily establish gut populations of beneficial bifidobacteria than could breastfed infants of *non-secretor* mothers.<sup>32</sup> In another study, higher levels of 2'-FL in human milk were associated with reduced risk for the infant developing immunoglobulin E (IgE)-associated allergic disease in infants delivered by Cesarean section.<sup>33</sup>

Dr. Guillermo Ruiz-Palacios (Mexico), National Institutes of Health Mexico, further emphasized the immune benefits of 2'-FL, by showing clinical evidence from studies of infants fed formula with added 2'-FL. Specifically, feeding with 2'-FL-fortified formula showed the following similarities to human milk feeding and improvements in comparison to formula lacking 2'-FL fortification: (1) weight gain similar to human milk-fed infants, and (2) reduced production of plasma proinflammatory cytokines, and (3) lower incidence of eczema.<sup>34, 35</sup>

## NECROTIZING ENTEROCOLITIS: PROTECTION BY THE HMO 2'-FL

**Dr. David Hackam (USA)** of Johns Hopkins University revealed why life-threatening necrotizing enterocolitis (NEC) is more likely to affect preterm infants than full-term infants. Surprisingly, the mechanistic link between prematurity and NEC is a transmembrane protein called a toll-like receptor.<sup>36</sup> Dr. Hackam described how toll-like receptor 4 (TLR4) is localized to the surface of specific cells. During gestation, TLR4 receptors are highly expressed on intestinal mucosal cells where receptor-mediated signals direct normal development of the intestine. After birth, TLR4 receptors are more highly expressed on the surface of cells of the innate immune system (e.g., macrophages and dendritic cells) where the receptors switch to a new signaling role for activation of innate immune responses. When a microbe binds to a TLR4 receptor on an infant's immune cell, downstream signals elicit an inflammatory response directing the cell to engulf and destroy the pathogen. However, in a premature infant, bacteria newly colonizing the intestine bind instead to TLR4 receptors still present on the intestinal epithelium. The ensuing response often leads to inflammation and death of cells in the infant's intestinal mucosa and disruption of the intestinal barrier, allowing bacteria to translocate to the bloodstream, and in some cases trigger sepsis—all part of the rapid-onset and often fatal condition NEC.<sup>36</sup>



**TLR4 receptors switch from fetal to neonatal expression patterns.** In gestation, TLR4 receptors are mostly expressed on intestinal mucosal cell surfaces (left, fluorescent green stain). After birth, TLR4 receptors are more highly expressed on the surface of immune cells such as macrophages, which bind and destroy pathogenic microbes (right, upper cells are macrophages; lower cells are rod-shaped bacteria).

**Dr. Richard Cummings (USA)**, a distinguished carbohydrate biochemist from Harvard Medical School, uses high throughput analytical methods to examine roles for glycans (i.e., oligosaccharides) and their cognate glycan-binding proteins. In particular, Dr. Cummings has catalogued the interaction of HMOs with an array of candidate binding proteins on the surface of intestinal cells, viruses, and bacteria. So what is the relationship between these HMOs and NEC in preterm infants? Results from recent animal and human cohort studies show that HMOs are protective against NEC.<sup>37</sup> This protection appears to be related, at least in part, to the ability of these HMOs to serve as “decoys” by mimicking cell surface carbohydrate chains on the intestinal epithelium; as a result, the pathogenic bacteria and viruses bind the soluble HMO “decoys,” thus preventing the microbes from binding to the mucosal cell surface and causing inflammation. Preterm infants fed with their mom’s milk or donor milk consume several grams of a structurally diverse blend of HMOs each day. Infants who are fed formula without HMOs do not have the same protective advantage. Dr. Cummings’ research studies aim to reveal which of the more than 200 HMOs found in human milk have protective potential that can be harnessed by adding them to infant formulas.

## NUTRITION FOR VISION AND COGNITION

**Dr. Lewis Rubin (USA)** opened the session by reviewing findings about the roles of the carotenoid lutein in vision and cognition, including its anti-inflammatory and neuroprotective effects.<sup>38</sup>

Dr. Rubin advised, “As humans evolve in a stress-filled environment, maintaining health requires a balance between (1) generating reactive oxygen species (ROS) and producing defensive mediators of inflammation and (2) removing potentially harmful ROS and preventing excessive inflammation.” Carotenoids, including lutein, are powerful antioxidants that cannot be synthesized by humans and must be acquired from the diet, in the form of dark green and yellow-orange vegetables such as kale and carrots. Lutein is selectively concentrated in human milk, and the infant’s developing nervous system relies on this source of lutein to prevent retinopathy and neuro-inflammation and promote healthy development.<sup>38</sup>

**Dr. Matthew Kuchan (USA)** further discussed the role of natural vitamin E (NVE), especially

in combination with lutein and the fatty acid docosahexaenoic acid (DHA).<sup>39, 40</sup> Like lutein, vitamin E is obtained from mom’s diet (in nuts, eggs, and leafy greens) and selectively localized in human milk and in the developing infant brain. Infants show rapid brain development, in terms of both brain mass and synapse formation. Infants with higher cord blood levels of NVE (the RRR stereoisomer of  $\alpha$ -tocopherol) at birth were found to have higher cognitive development at 2 years of age.<sup>41</sup> Expressed together in synaptic membranes, lutein and NVE protect membrane lipid components (e.g., DHA) from oxidation and promote neurite growth.<sup>42</sup> Because of this combinatorial effect, preclinical studies are now underway to examine whether formulas supplemented with lutein, NVE, and DHA will promote brain and eye development similar to human milk.

ESPGHAN 50<sup>th</sup> ANNUAL MEETING  
of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition

Welcome to Prague

Pediatric Nutrition News  
Sean M. Garvey, PhD, Editor  
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