



Intestinal Microbiology of Early Life

Close Encounters of a Symbiotic Kind

Prof. dr Jan Knol

Inaugural lecture upon taking up the post of Special Professor of
Intestinal Microbiology of Early Life at Wageningen University
on 30 May 2013



WAGENINGEN UNIVERSITY
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Close Encounters of a Symbiotic Kind

Dear Rector Magnificus, dear colleagues, family and friends.

Welcome everyone, thanks for coming, good to see so many of you. Special thanks for those coming from far, whether it's Stad en ommelanden, Cambridge, Boston, or Singapore.

And I can tell you, we are not alone! Living in a microbial world, I am pretty sure that all of you brought at least your kilogram of microbes with you. Actually, each and every one of us is hosting a number of gut bacteria that is higher than the number of people that ever lived on this planet.

I am glad you could all make it today.

Introduction

In this lecture I would like to focus on an important event in all our lives, and that is when we had our first encounters with the microbes around us. Biologically it must be an amazing transition from the sterile and well protected environment of the womb to the immediate exposure of countless numbers of microbes in the new environment we enter into.

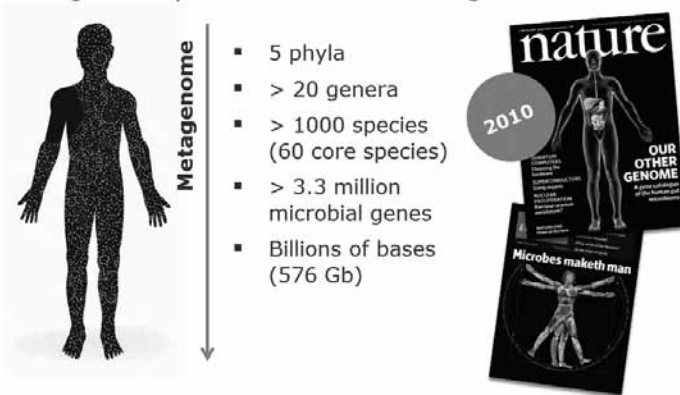
Fortunately, nature gave us human milk as first nutrition to guide us through this very important first phase of life. Clearly human milk contains calories, macro- and micronutrients, but also very important components that guide our physiological development in early life. Human milk therefore should be regarded as the first and most important choice of infant feeding. Maybe even more so considering the microbial world we live in. Actually, we are only since very recently aware of the microbes around us. A bit of history...

Intestinal microbiology

It was only about 300 years ago that Anton van Leeuwenhoek discovered 'small animalcules' as he called them, on different body sites. He was only able to do so, because he managed to make lenses that did not exist before. One of the things he studied was the white layer between his teeth, and he wrote: *"I found to my great surprise that it contained many small animalcules, the motions of which were very pleasing to behold"*. The field of gut microbiology developed soon thereafter.

At the end of the 19th century, Theodor Escherich, was already the first pioneer in Intestinal Microbiology of Early Life, as he studied the role of gut bacteria in the ology of infant digestion. And it was Nobel prize winner Mechnikov who stated already in 1908: *"When people have learnt how to cultivate a suitable flora in the intestines of children as soon as they are weaned from the breast, the normal life may extend to twice my 70 years"*. We are not there yet, but the understanding of the complexity of the gut microbiota has grown considerably.

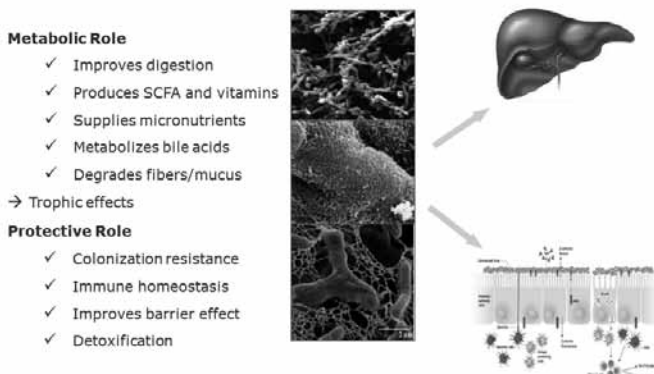
Full gene repertoire of the adult gut microbiota



In 2010, a milestone paper was published in Nature by Dusko Ehrlich and many co-workers including Wageningen University and Danone Research (Now Nutricia Research), describing a human gut microbial gene catalogue that led to some new and surprising insights. We already knew that 90% of the cells in our body are actually microbial, but the number of genes present in the gut microbiota of a healthy adult reaches numbers that outnumber the human genome by a factor of more than 150. This metagenome, or also referred to as 'our other genome', contains sequences of 5 major phyla, overall more than 1000 species of which each individual carries at least several 100 species. Besides bacteria, also significant numbers of archaea, viruses and eukaryotic cells can be found in this ecosystem.

The human gastrointestinal tract plays a central role in human physiology. In the gut, the major biological systems of the human body come together and interact. In this interface with our external environment of about 300 square meters, 60-70 % of the immune cells can be found, about 100 million neurons are present, and the gut contains 100 trillion microbes. It's of course also the organ where our food is digested and absorbed, which makes it reasonable to believe that with nutrition we can indeed directly impact these important physiological processes.

Gut Microbiota, essential role in human physiology



The activities of the gut microbiota are diverse and critical for human health. The microbes with their high numbers and unique physiological capacities are thought to be as metabolically active as our liver. These activities range for example from the digestion of food, to the production of different short chain fatty acids and vitamins, impacting the bioavailability of micronutrients, metabolism of bile acids and degradation of mucus. These effects are important in the gut directly, but for example the metabolites can be transported throughout the body and have important trophic effects as well. Besides these metabolic effects the gut microbiota also plays an important protective role. The microbes present in a healthy gut do prevent the colonisation of less desired organisms by nutrient competition or with direct anti-microbial mechanisms for example. Due to the cross talk of the microbes with the host at the molecular level an immune homeostasis can be maintained that is also important for systemic immunity. The microbes can have direct effects on the barrier function of our intestinal wall and protect the gut from becoming leaky and less selective as a barrier. The microbiota can also protect the body of the host by detoxifying components from our diet that may otherwise be harmful.

As an example of the importance of the gut microbiota in health and disease the link between microbes and obesity is an interesting example. Research has shown that associations can be made between gut microbiota and overweight. Turnbaugh and others have linked obesity with shifts in microbiota composition, but more importantly that the transfer of the microbiota of obese mice to germ free mice also led to excessive weight gain in the recipient animals. This may indicate a cause effect relationship, and interestingly similar experiments recently performed in humans show that indeed human physiology is also impacted by transferring the microbiota of lean individuals to individuals with severe obesity. This is one example, but we get more and more evidence, although quite often from animal studies, that the microbiota is not only associated with physiology or diet of the host, but is indeed also effecting important physiological parameters directly.

Intestinal microbiota: the start

So how does the gut microbiota develop after birth? What happens immediately after birth is actually pretty amazing.

It all starts as a sterile surface, but after some first colonisers the first hours and days, a complex ecosystem already establishes after a few days or weeks.

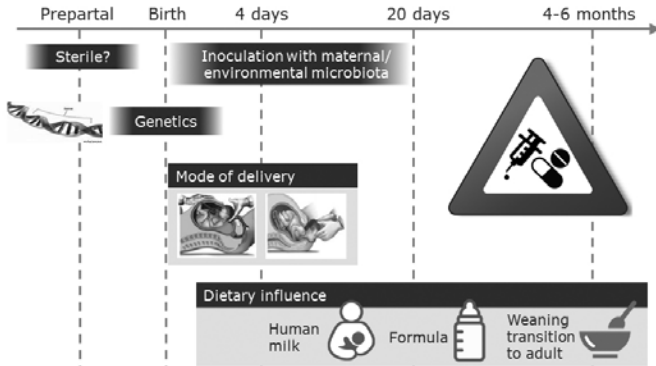
Before birth the fetus is thought to be in an essentially sterile environment, although some recent data suggest that this may not be entirely true, and that even in amniotic fluid exposure to microbes or microbial signals may already occur. But only during birth infants are inoculated with significant numbers of maternal and environmental microbes and the microbiota starts to develop.

It has been shown that the microbiota of closely related family members is more similar than of people that are not related, so genetic factors of the parents seem to play a significant role.

To indicate the importance of early exposure it is worth mentioning that differences are observed between the microbiota of infants born vaginally and those born by caesarean delivery.

After birth several factors are important for the next steps in the development of the microbial ecosystem in the gut. One of the main drivers during the first weeks is of course the diet and human milk as a natural source of nutrition seems particularly important for the colonisation process. This is seen especially in the first months of life when infants are exclusively receiving human milk. When solid foods are introduced the microbiota becomes more divers and more similar to the microbiota of adults. When the microbiota is fully established is unclear and the composition

The early intestinal microbiota

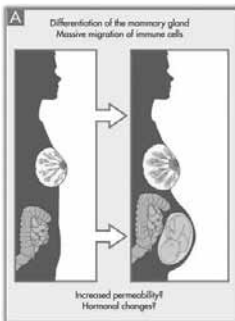


remains also dynamic throughout life. However, in general adults can be identified by their microbiota profiles over longer periods of time.

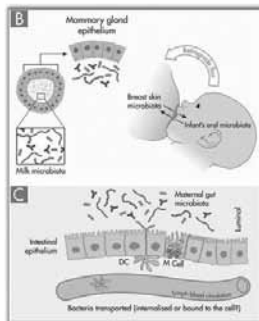
One factor that has become very important the last 100 years is the use of medication and drugs, more specifically antibiotics that are used frequently in hospital settings, can have a major impact on the developing gut microbiota.

Human milk a source of life

Physiological changes during pregnancy



Potential routes



One may consider the process around birth as a microbiota transplant from mother to child. The importance of the different routes are unclear, but may involve transfer through amniotic fluid, direct transfer during delivery or thereafter, but also with human milk as an important source of microbes.

Important contributions to our recognition of human milk as a source of microbial life have been made by Juan Miguel Rodriguez, Rocio Martin and others. They have consistently found that microbes are present in human milk. Numbers are relatively low, but for inoculation of the young infant the viable cell count is probably high enough to be biologically significant. During pregnancy important physiological changes take place and one of the hypotheses is that microbes can migrate from the gut, which becomes more permeable around delivery, to the mammary gland. It is striking that already the first milk produced can contain microbes. Migrating immune cells that travel from the gut to the mammary gland may act as vehicles for even viable microbes. Another route that may be important is the retrograde flux from the baby's oral cavity to the mammary gland, or microbes from the mother's skin. The exact biological role and relevance needs to be studied in more detail, as well as the impact on the developing gut microbiota of the infant.

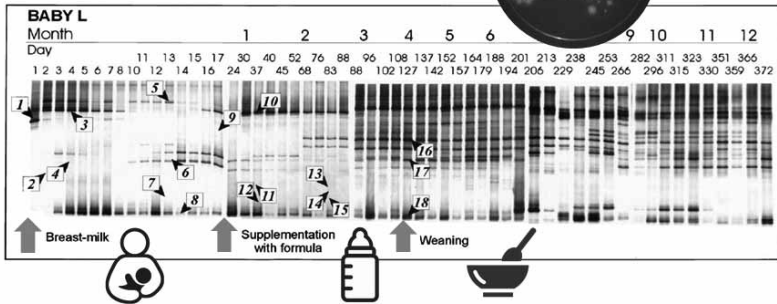
In a collaborative study that we performed with Makino and others, we were able to show that specific strains of *Bifidobacterium longum* can be identified in mothers and their children, but not in other unrelated individuals. In some cases the specific strain could already be detected in the faeces of the mother 2 months before delivery, in the infant at one month of age, and in the breast milk of the mother, indicating direct and specific transfer of gut microbes from mother to child.

Some of the pioneering work on early colonisation was done some 10 years ago in the Laboratory of Microbiology of the Wageningen University, by Favier, de Vos and co-workers. With molecular microbiota fingerprinting tools the dynamics in early life were monitored and the impact of breast milk, supplementation with formula, and the introduction of solid weaning foods were studied. Important advantage of these technologies is that it is no longer needed to culture live bacteria, something that is still today very difficult for many species residing in the gut. Indeed the development of new technologies, mainly molecular biology tools, has greatly accelerated our understanding of the complexity and dynamics of the gut microbiota.

Recently a similar study was performed, but where samples were now analysed with next generation sequencing technologies. In this study the authors describe the changing microbiota and the microbiota becoming more and more complex. The phylogenetic diversity is increasing the first 1000 days of life and does not seem to reach a plateau and is still significantly lower than the diversity of the faecal sample of the mother. In this study also the significant impact of antibiotic use in early life was demonstrated, showing that the microbiota at this stage is rather sensitive for this kind of perturbation. The authors also determined the bacterial genes present in the faecal samples of the infant during the first year of life and demonstrated a

Microbiota Fingerprint

Dynamic in early life



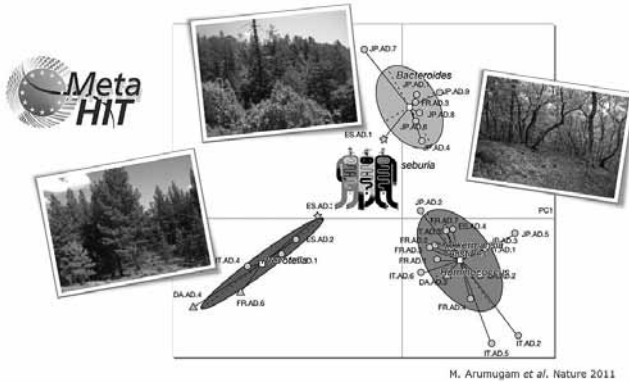
Favier et al., Appl. Env Microbiol 2002, 68:219-226

significant shift during the period where solid weaning foods are introduced. The microbiota at this point is adapting to the diet that is very different from the milk diet. Complex fibres, new protein and fat sources induce a major change of the microbiota, bringing the metabolic capacity of the microbiota closer to the faecal microbiota of adults. Since weaning foods are introduced gradually, the microbial ecosystem is adapting accordingly.

It is known that the microbiota composition of different individuals can be very diverse when looking at types of bacteria present. So the diversity can be very different and the bacterial phyla can vary significantly, but when we determine the genes present in the gut microbiota we see that the overall activities encoded by the metagenome are rather stable and similar also between individuals. From this we can probably conclude that the taxonomic composition of the microbiota may be very different between individuals but that the overall functionality of different microbiotas is rather similar. So, different combinations of micro-organisms can deliver similar functionality to the ecosystem, and there are many solutions to have a microbiota that encodes the full functionality necessary for the symbiosis with the host.

More recently, within the EU program MetaHit, in a larger number of individuals the metagenome was determined and it appears that people can be clustered based on their microbiota composition; these clusters are referred to as enterotypes. We could compare this concept with another complex ecosystem like a forest. Every forest is very different but still we can recognise specific kinds of forest, like: needle leaf, broad leaf or mixed forest. Whether the enterotypes are really distinct, whether there are only 3 types, or whether these are stable in an individual, remains to be

Distinct microbiota types in adults: Enterotypes



determined. But, if specific gut microbiota types exist one could think of more personalised nutrition concepts, targeting the composition and activity of these specific microbiotas. What exactly drives the formation of enterotypes in early life is unknown, but probably depends on factors like genetics, diet, drug intake etc. It would be interesting to understand these processes better, as there are some indications that specific enterotypes may be more prone to certain diseases.

Although the enterotypes were demonstrated around the globe, the specific microbiomes still can be significantly different based on geography. Last year significant differences in the microbiota of individuals from North America, South America and Africa were described. What could explain these differences and whether these differences are relevant for health remains yet unclear.

Gut microbiota and the immune system

For microbes to propagate in the gut a good relationship with the host is key. An important player in these interactions is the human immune system. Micro-organisms have dominated life on earth for billions of years, and are still the largest fraction of living biomass on this planet. For the species *Homo sapiens* to evolve the last 200 thousand years, it has been essential to adapt and anticipate to the microbial world already existing, and to adapt to the microbial challenges and opportunities around us. So the first encounters must already have been of a friendly kind, but it was essential to develop an immune system that is able to safeguard the symbiosis. Today we need to be in homeostasis with our microbiota, for richer for poorer, in sickness and in health.

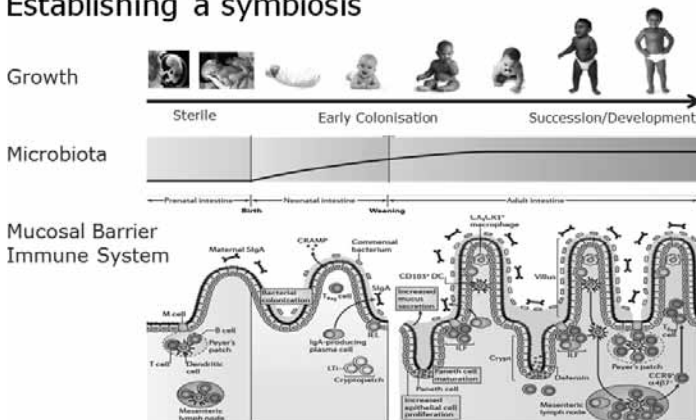
There are very convincing studies in rodents that show the impact of microbiota on the developing gut. Comparing germ free animals to colonised animals shows big

impact on gut morphology, the formation of blood vessels, and the composition of the mucus layer for example. The mucus example is particularly interesting, since the microbes seem to be able to manipulate the host to produce exactly the kind of mucus that is preferred by the microbes as a substrate for growth.

The co-development of the microbiota and the host in early life is an important but still largely unknown process. To prevent rejection of the fetus by the mother, the immune system of the infant is suppressed and underdeveloped at birth. The maturation of the immune system is for a big part taking place in the first months and years of life, exactly the period when human milk is the most important component of the diet. It is well accepted that human milk contains many different factors that can steer this process in a most optimal way. It is also the period when the gut is colonised by microbes and the gut immune system is maturing and a symbiosis is established. Different immune cells are triggered by the entering microbes, and the developing immune system is impacting the microbiota composition. One major role of human milk is the impact on the composition of the early microbiota and safe guarding the symbiosis. This cross talk and co-development in early life is probably crucial for the establishment of a stable microbiota contributing to human health throughout life.

Indeed it has been shown that the microbiota of allergic vs non allergic infants can be different. Allergic infants seem to have a more adult type of microbiota already early in life, with species like Clostridia, E. coli, and other enterobacteriaceae. In healthy breast fed infants the microbiota is rather dominated by bifidobacteria, lactobacilli, and some others. Interestingly some of these differences have been observed before allergic symptoms become apparent. However we should be careful not to over

Establishing a symbiosis



interpret these data. For example a species like *E. coli* found more predominant in allergic infants, can have very different impacts on the host. On the one hand *E. coli* Nissle is used as a probiotics to improve health, whereas another strain, also known as the 'hamburger *E. coli*', can cause severe disease and even death. This also indicates that looking at the microbiota from a taxonomic point of view is limiting our knowledge and we should therefore always regard the functionality of microbes in a specific ecosystem. Indeed, a microbe's effect on the human body can even depend on specific local conditions. If we better understand the human body as an ecosystem it may be possible to influence the system and prevent many diseases, from acute diseases like infections to chronic conditions like inflammation, and maybe even mental health.

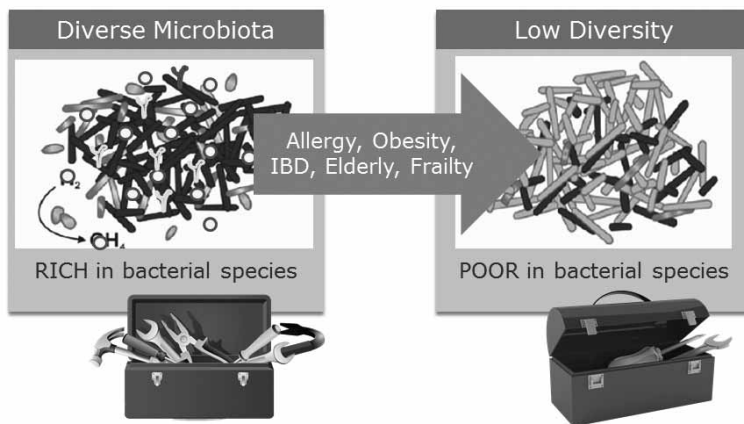
Immune diseases like asthma, eczema or hay fever are very important today. Over the last decades the incidence has and is still increasing in many countries around the world.

One of the ideas to explain the increase in immune diseases is the so called hygiene hypothesis. Due to changes in our societies, which have become much cleaner and more sterile, the immune system is not triggered and challenged enough to develop the right response when an allergen is encountered. Only a few decades ago, I think the picture on the left is around 1970, children were more exposed to microbes, as today infants can sometimes enter the world under almost sterile conditions.

The hygiene hypothesis is now shifting somewhat as it is not only the exposure to potential pathogens, but more the exposure to a decreased microbial diversity in our living environments. If the host is susceptible, this lower exposure is thought to lead to inappropriate activation of the immune system that can cause chronic inflammatory diseases.

What is gut microbiota diversity and what could be the consequence of a lower microbial diversity? It seems that a healthy microbiota is highly diverse and contains many different species. The microbiota is well equipped and all phenotypic relevant traits are present in the ecosystem. This requires a good alignment with the immune system that has to recognise and allow the stable persistence of many different gut microbes to allow homeostasis. However, if species diversity is lost the gut microbiota becomes less well equipped, probably more vulnerable for challenge and less resilient for external factors that impact the composition and overall activity. There are indications that in diseases like allergy, obesity, and inflammatory bowel disease, but also in frail elderly the gut microbiota diversity is indeed significantly decreased.

Gut microbiota diversity!



Comparing again with the forest ecosystem, we could envision that when the ecosystem is disturbed by for example burning the rain forest the environment becomes sensitive for erosion. Something similar may happen when for example strong antibiotics are used to treat infections that the gut microbiota is compromised, and becomes less resilient for challenges making the host more susceptible for disease. Since the microbiota in early life seems to be specifically sensitive for disturbances, and considering the fact that this is the period where the symbiosis is established we may need to consider the impact of caesarean deliveries and antibiotic use in early life which still seem to be on the rise around the globe.

Recent data from De Weerth and co-workers in collaboration with the Lab of Microbiology of the Wageningen University show a correlation of specific microbiota signatures with colics in young infants. Infants with colic indeed showed lower microbiota diversity and stability than did control infants. The microbial signatures could potentially explain the excessive crying, which could be another example of the importance of intestinal microbiology in early life.

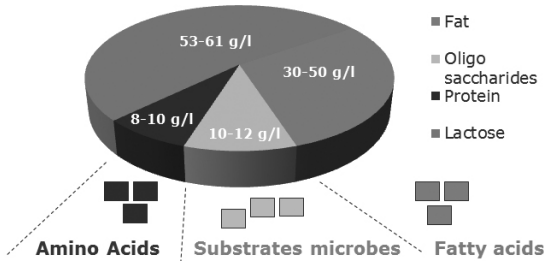
Gut microbiota and nutrition in early life



So is nutrition a factor and can we use nutrition to impact the intestinal microbiology in early life?

It has already been known for more than 100 years that breast fed babies, especially in the first months of life, can have a different microbiota than infants receiving a formula based on cow's milk. The microbiota of breast fed babies (here on the left) is generally high in bifidobacteria, lactobacilli and some other species. Cow's milk

formula fed infants however (panel on the right), can have already a more adult type of microbiota with higher percentages of *E. coli*, clostridia and eubacterial species. These differences have mainly been attributed to the differences in composition of human milk vs cow's milk. Human milk is rich in lactose, protein and fat, but also contains high levels of complex human milk oligosaccharides, that are virtually absent in cow's milk. The oligosaccharides are probably a major modulator of the intestinal microbiota as these are important growth substrates for gut bacteria.

Human milk contains microbial substrates



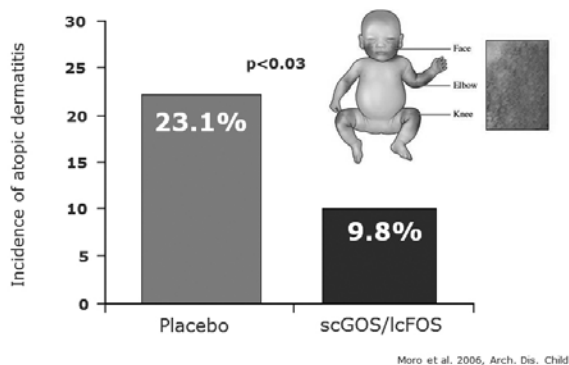
	Human milk 	Cow's milk 
Lactose	55-70 g/L	40-50 g/L
Total oligosaccharides	3.0-15.0 g/L	Traces

Although these human milk oligosaccharides are not available today for the manufacturing of foods, we do have alternatives to modulate the intestinal microbiota. The main ones are listed here. Prebiotics which are essentially growth substrates for specific microbes in the gut. Probiotics, which are actually viable microbes that are added to the diet. And synbiotics a combination of these two.

In recent years a prebiotic mixture has been developed and tested in infants, that is indeed able to modulate the gut microbiota in early life. We see a dose dependant increase of bifidobacteria in infants receiving a milk formula with added prebiotics, to reach levels also observed in breast fed infants. The prebiotics used are a mixture of galacto- and fructo-oligosaccharides in a concentration that is comparable to oligosaccharides in human milk. Not only is the bacterial composition impacted by these interventions, also the gut physiology is significantly altered; short chain fatty acid profiles and pH for example become very similar to values observed in breast fed infants. This is a clear example that early nutrition can impact gut microbiota composition and activity.

Knowing that we are able to modulate the microbiota and making it more similar to that of breast fed babies we were interested to see if these prebiotics could also have an impact on the immune system and immune disease symptoms. For this a prebiotic formula was given to infants that have a high risk of allergy, based on family history of allergic disease. In this population it was shown that it is indeed possible to significantly reduce the incidence of atopic dermatitis with a prebiotic intervention targeting the gut microbiota.

Prebiotics can reduce atopic dermatitis symptoms



But do we understand how??

Not really. In order to understand how microbes in the gut can impact the host, many questions remain. For example there is the major difference between the different parts of the gastro-intestinal tract. The small intestine for example is quite different from the large intestine. Numbers of immune cells, bacterial populations, gut morphology, mucus quantity and quality, all are very different. For practical reasons most studies focus on the faecal microbiota, which is more representative for the large intestine, although physiologically the small intestine is probably even more relevant. To study the microbiota in the small intestine remains very difficult because sampling is almost impossible, especially in young infants.

Intestinal microbiology of early life: the future

Even if we start to know where the important host-microbe interactions take place, we still have a challenge to pin point the interactions that really matter. In the gut many different cell types are present, all of which express many different receptors that can interact with all kinds of different molecules expressed on the surface or secreted by gut microbes. Interesting work on this molecular host microbe interaction is done by Professors Wells and Kleerebezem also at this University.

The challenge for the future will be to understand the impact of these interactions and to find the right buttons in the gut that we can impact with nutrition, in order to bring health benefits.

Specifically regarding the microbiota development in early life some important scientific questions can be formulated. For example:

When and how do we really acquire our gut microbes;

Is the maternal microbiota essential?

Is it a change process or are conserved biological mechanisms directing this process?

What drives the development of the microbiota after birth?

What is contribution of: diet, antibiotics, gestational age, caesarean vs. vaginal, geography, etc?

What could be appropriate microbiota markers for health and disease outcomes?

Bacterial species, specific genes, RNA, proteins or metabolites?

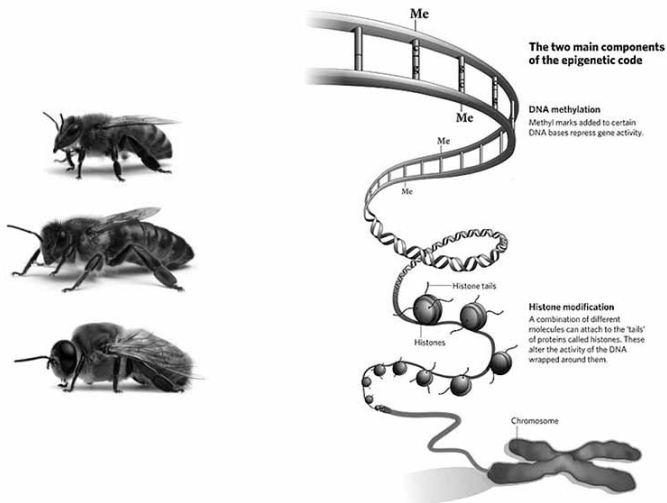
When do specific signatures predictive for disease appear in the microbiota and what drives the development of these signatures?

If we understand the microbial ecosystem better can we improve our nutrition to improve our health? Could we in this way support or improve immune function, metabolic development or neurological outcomes?

Some of these questions I hope to address the coming years, given also the opportunity within the special chair of Intestinal Microbiology of Early Life. The challenge will be to go from taxonomic mapping to functionality of the microbiota. Omics- technologies, like transcriptomics, proteomics or metabolomics, will certainly catalyse our further understanding of the gut microbiota.

Our genome is more or less fixed, but still the environment can have a major impact on the development during the life span. Processes like epigenetics are particularly interesting and we are just starting to understand how DNA methylation and histone modification mechanisms can regulate gene expression and confer phenotypical

Epigenetics and nutrition, an example...



changes. Clearly the first 1000 days in life are very important, since this is the period where we encounter external stimuli for the first time and the body is trained to respond to these stimuli. And where our genome is fixed, we can still influence the epigenome and our microbiota.

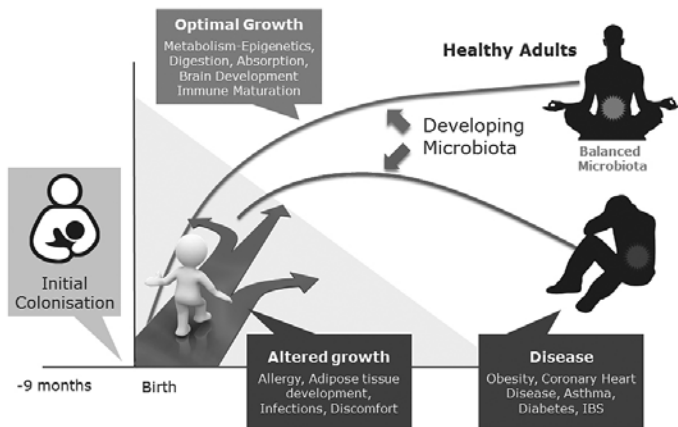
We do have a great example in nature. Where all bees are born genetically identical, dependent on the type of nutrition, the insects can develop very differently. Only if they get the best nutrition they become a Queen.

Knowing the importance of the gut microbiota for human physiology, the incredible development of infants in the first years of life, and the concurrent colonisation of the body with microbes makes us believe that the Intestinal Colonisation in Early Life may be very important for health also in later life. Whether immunological, metabolic or neurological, all these systems are developing at this period.

Disturbances in early life may lead to altered growth, immune diseases like allergy, metabolic diseases like obesity or cardiovascular diseases and maybe even brain and behavioural problems. Nutrition in early life and acquiring the essential microbes is probably a critical factor in this process.

For this reason it may be important to study the symbiosis over several generations. If the symbiosis in individuals is disturbed this may lead to a compromised gut

Developmental Microbiology



microbiota in the next generation and a significant effect on health may be amplified over several generations. Considering the importance of the maternal microbiota, the increase of caesarean deliveries and antibiotic use in infancy may impact the symbiosis especially over several generations.

A symbiosis that could catalyse our understanding in this field is the combination of Wageningen University and Danone Research. Considering the mission of Wageningen University ' to explore the potential of nature to improve the quality of life' , and the mission of Danone ' bringing health through food to as many people as possible' , I am happy to be working on this interface. And although Danone Research will move to Utrecht soon I trust we will even have many more close encounters in the future. With the knowledge and specific expertise on both sides, we should be able to generate Science for Impact. I am really grateful for the support of both the Danone Baby Nutrition (Now: Nutricia Early Life Nutrition) and Nutricia Advanced Medical Nutrition organizations to support this special chair.

In the 1977 movie of Steven Spielberg close encounters of the first kind were defined as sighting of the unknown. I guess this privilege was for Antonie van Leeuwenhoek. By now we have had our close encounters of the second and third kind. We have accumulating evidence for life in our gut, and we clearly recognise that we are in contact with our microbes at all times. I guess the challenge for the future will be to have close encounters of the fourth kind: maintaining the symbiosis. So please remember, we are not alone!!!

Dankwoord

For the last part of my lecture, maybe the most important part since I want to thank the people that made this appointment possible, I will switch to Dutch.

Dit laatste deel van de rede, waarin ik een aantal mensen wil bedanken, spreek ik graag grotendeels uit in het Nederlands.

Allereerst wil ik het bestuur van Wageningen Universiteit, de Rector Magnificus Martin Kropff en de benoemingscommissie onder voorzitterschap van Marcel Zwietering, bedanken voor mijn benoeming en het in mij gestelde vertrouwen.

Ik kan me mijn eerste bezoek aan het Laboratorium voor Microbiologie nog goed herinneren. Onaangekondigd was ik met een collega op bezoek bij een van de onderzoekers, de helaas overleden Anton Akkermans. Destijds was al duidelijk dat Prof. Willem de Vos zeer betrokken is bij het reilen en zeilen van de organisatie, en dat is nog steeds het geval. Willem ik bewonder je energie en snelheid, en wil je hartelijk danken voor de aanstelling binnen je leerstoelgroep.

Also a special word of gratitude to Florence Jeantet, also representing Danone Baby Nutrition. Florence, you have been a great coach, student, and supporter. Merci beaucoup.

En Hanno Cappon, ook jij hartelijk dank voor alle support en de support van Nutricia Advanced Medical Nutrition.

Ook de hoogleraren in de leerstoelgroep Microbiologie, John van der Oost, Fons Stams, Vitor Martins dos Santos (chair systems and synthetic biology) en in het bijzonder Hauke Smidt wil ik hartelijk danken. Het is makkelijker om in een goede organisatie je weg te vinden, en de wetenschappelijke kwaliteit is buitengewoon. Nu de kwaliteit van de pizza's nog.

Clara Belzer, dank je wel voor al het werk dat je hebt gedaan om mijn start binnen het laboratorium efficiënt te maken, en Lennart Jongjans en Romy Zwittink dank voor jullie enthousiasme en voortvarende start. Ik kijk uit naar onze verdere samenwerking.

Dan mijn mentoren van het eerste uur: de hoogleraren Wil Konings, Bert Poolman, en Tjakko Abee. Dank voor het stimuleren van mijn wetenschappelijke nieuwsgierigheid en de solide wetenschappelijke basis.

Also a big thank you also to the speakers of today's scientific symposium, thanks for coming and to share your scientific expertise with us. Muchos Gracias.

Speciale dank ook voor de mensen van de communications afdeling van Danone Research. Mirjam, Heather en in het bijzonder Saskia Knol, geen familie, voor de organisatie van deze dag.

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Dear colleagues at Danone Research and especially within the Life Science department it is a pleasure to collaborate in this exciting field of nutrition and health, and to be able to have all the multidisciplinary interactions. I am already looking forward to our new adventure @de Uithof and the research teams in Singapore and Shanghai. Hans Leijtens, special thanks for you making our managerial lives easier, and I am happy to see that you now recognize that there is more literature than the economist.

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Ik heb gezegd.



Prof. dr Jan Knol

'When a baby is born it enters a microbial world where micro-organisms are everywhere. Indeed, within the first days the human body becomes host of a complex community of micro-organisms that form an essential part of our normal physiology. The impact of the microbiota ranges from immune effects, metabolic interactions, to maybe even brain and behavioural effects. The initial colonisation after birth is a unique process, but do we fully appreciate the benefits of this symbiosis that is being built and are we able to protect it?'