

“MESSAGE IN A BOTTLE”

Inaugural speech to accept his office as Professor
"Food-borne Risk Factors for Allergic and Inflammatory Diseases"
in the faculty of Medicine at the Utrecht University

pronounced by Prof. dr. Geert Houben on 8 May 2018

Mr. Rector Magnificus, dear colleagues, dear friends and family, value listeners,

When in the summer of 1981, with my diploma from the VWO in my pocket, I put my stuff in a van and left for Utrecht to study biology, exchanged my Limburg running rounds for Utrecht running rounds, and my weekly dances on Led Zeppelin or The Police replaced by dancing 3 or 4 times a week at Led Zeppeling or The Police and blues jam evenings in the basement of 't Oude Pothuys on the old canal, an unprecedented disaster took place in Spain. In a short time, more than 20,000 people were affected by a mysterious illness. They developed a mixture of serious symptoms, including severe lung problems, heart complaints, vascular and nerve disorders and skin abnormalities. Approximately 300 people died shortly after the onset of symptoms and probably about 300 in a short period thereafter. Large-scale investigations were started, with the World Health Organization quickly taking a coordinating role. Initially, it was thought to be an infectious disease, but gradually it became clear that the disease was related to the consumption of a specific olive oil.

This was no ordinary consumption oil. It was an oil that was not meant for consumption but for industrial applications. To prevent consumption, aniline had been added to this oil, which made the oil taste dirty and had a bad odor. Fraudulent traders, however, had figured out that they could extract the aniline from this cheap oil by refining and then sell the oil as expensive consumption oil. They had succeeded in getting the aniline and thus the bad taste and smell out of the oil, but something had gone terribly wrong, witness the mass poisoning that resulted from the consumption of this oil. The poisoning cases were closely related to the occurrence of a number of substances arising from the heating of the substance aniline during the refining process. It is generally assumed that this mix of disorders, later referred to as the Spanish Toxic Oil Syndrome, is caused by reaction products of aniline. Most of the approximately 20 thousand survivors developed chronic diseases that continue to this day. Approx. 3.5 thousand people have permanent total disability. The disorders developed by the poisoned people turned out to be autoimmune diseases: inflammatory diseases that arise because our immune system starts to attack the body's own structures, which damages cells and tissues and functions in our body. Something in the oil had caused these disorders in tens of thousands of people, but to this day it has not been determined with certainty what caused this poisoning. We did not actually have any methods to unlock the information in those bottles of oil and to determine the exact cause; to read the "MESSAGE IN A BOTTLE". When I heard of this disaster in the middle of the eighties and talked about it with my later promoter Prof. dr. Willem Seinen, I became fascinated by the fact that something could cause such a disastrous disruption of our immune system through our diet and my interest in food toxicology and immunotoxicology was triggered.

The processes that cause damage to our cells and tissues in autoimmune diseases are inflammatory processes. Inflammatory processes are necessary to ensure our health and are the central battle tactics of our immune system. For example, they play a central role in the prevention of infections and the removal of damaged cells in order to prevent cancer formation. But our immune system can also overshoot and react to substances that we receive through, for example, our inhalation air or our diet or by reacting to structures of our own body. The inflammatory processes can then lead to allergies or to autoimmune diseases, such as in the case of Spanish Toxic Oil Syndrome. You can combat these kinds of inflammatory diseases by suppressing the immune system. The downside, however, is that this usually goes hand in hand

with a weakening of defence functions that are necessary again, resulting in an increased susceptibility to infections for instance.

The immune system is a balance that continuously balances between responding and not responding, not responding too quickly and not too late, not too strongly and not too weakly, between useful inflammatory reactions and harmful inflammatory reactions, between protection and disease. And actually this is still a too simple representation of things. It is actually a complex structure of many balances, with an increase in one function, usually being accompanied by increases in a number of other functions, and decreases in again other functions. Optimal balances in this system are therefore of great importance. And that does not always work well. More than 2.5 million people in the Netherlands suffer from chronic inflammatory disease, while in roughly half of all disorders that are not primarily classified as immunological disorders, inflammatory processes also play a central role. Think of cardiovascular diseases, diabetes, many cancers, infectious diseases ...; inflammation processes play a crucial role in all these disorders. It will be clear to you what the impact is of a malfunctioning immune system or disturbed balances in it.

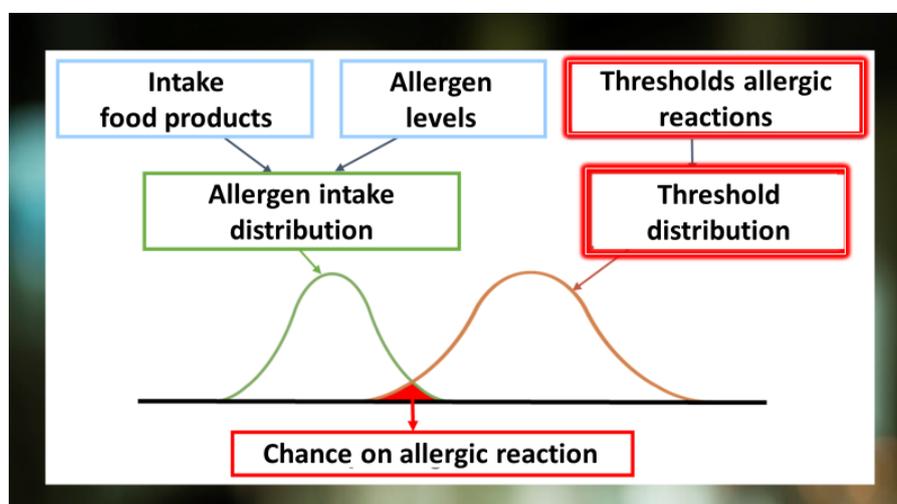
The functioning and balance sheets of our immune system are determined and influenced by many, partly unknown, intrinsic factors, factors in our body, such as our genetic predisposition. But in addition, many extrinsic factors, factors that affect us from the outside, have a strong influence on our immune system. And to make it even more complex, many intrinsic and extrinsic factors influence each other and interact with influencing the immune system. But we hardly know and understand these influences. This also applies to factors in our diet; one of the most important sources, or perhaps the most important source of exposure to microorganisms and substances. Our food contains thousands, if not hundreds of thousands of substances. My chair aims to gain a better insight into the risk factors in our food that play a role, and how they play a role, in allergic diseases and inflammatory diseases and on this basis find starting points for better prevention, diagnosis, therapy and management of these diseases.

One of the most clear and appealing examples of a role of food in allergic or inflammatory diseases is I think food allergy. Food allergy is a condition that occurs in about 3% of the western population; that equates to more than half a million people in the Netherlands. This means that food allergy is one of the most common disorders. In addition to the people who directly affect it, 4 to 5 times as many people in their area are affected by food allergies; think of family, friends, colleagues, catering staff, etc. There is no therapy for food allergy available, while medicines can only be used to suppress a reaction in case of emergency. Avoiding the substances for which one is allergic is therefore the only thing that really helps, or ... I have to say, what would really help, because in practice this is often very difficult, if not impossible.

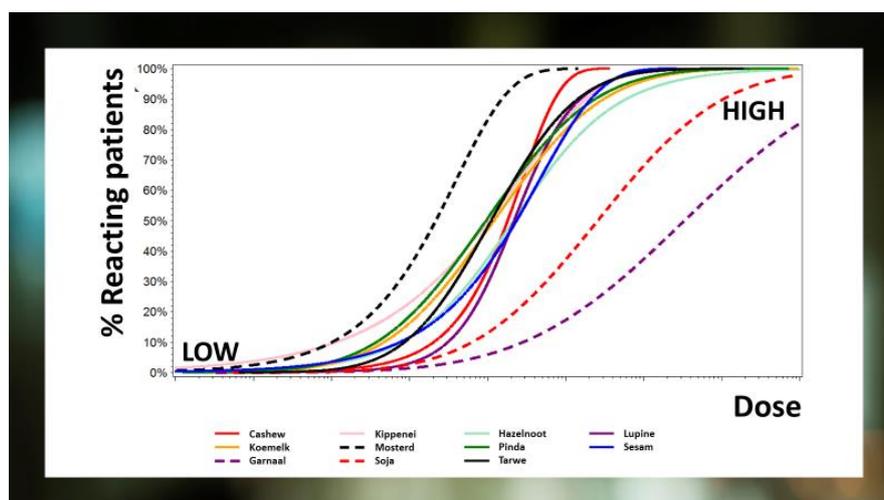
Various studies have shown that the presence or absence of a warning on labels of foodstuffs has little or no correlation with the presence or absence of the substances for which one may be allergic; ... say, the "message on a bottle" does not match the "MESSAGE IN A BOTTLE". This makes food for the food allergic consumer to Russian Roulette. People with food allergies therefore regularly have unexpected allergic reactions, not uncommonly, probably in many thousands of cases per year, with Emergency Room assistance needed as a result, despite the fact that many foodstuffs are already being retrieved before they reach the consumer at all; 40 to 50% of all food recall operations are related to incorrect or incomplete information about allergens. A large number of safety standards have been adopted internationally for chemical substances and micro-

organisms in food. There are no adequate regulations regarding allergens in food. And this while the impact of allergens in food on public health seems to be many times greater than that of known chemicals and micro-organisms that can occur in food. The annual loss of healthy life years in the Dutch population by known chemical substances and micro-organisms in food is estimated at a few thousand by the Dutch National Institute for Public Health and the Environment; for allergens in food, this is estimated to be several tens of thousands. This brings me to the first major research theme that the UMC Utrecht and TNO teams are working on and I want to continue to work hard for in the coming years: establishing better regulations for labeling allergens in food and improving care for food allergy patients.

What is the problem with the regulation about allergens in food? Legally it has been regulated that food manufacturers must state on a label if ingredients from important allergenic foods, such as milk, egg or nuts, have been incorporated into a product. However, allergens can also unintentionally end up in food. For example because some peanuts remain in a lorry in a load of soy, or because some milk residues of milk chocolate are left behind in pipes in which, after milk chocolate, plain chocolate, which does not have to contain milk, flows through a factory. Manufacturers who cannot exclude these risks or are afraid of these risks often warn against this on the label. You know the sentences: "can contain traces of peanuts", "is made in a factory where also milk is processed", "can contain soya". A consumer with an allergy to one or a few foods is faced with a dilemma. To eat or not? You might think not. But it is not that simple, because I have told you before that the presence or absence of a warning shows little to no correlation with the presence or absence of allergens. Various studies and monitoring programs have shown that in products with a warning in 7 to 93% of the cases indeed the allergen for which is warned is found. This means, however, that in 7 to 93% of the cases the allergen for which is warned is not found. And unfortunately, products without warning appear to contain allergens in 11 to 53% of the cases. This is one of the causes of the previously mentioned large number of unexpected allergic reactions that affect the food allergic patient. This is a situation that emerges structurally in various studies and various countries during the past 10 to 15 years. This can and must be changed. However, it is not possible to exclude all risks, and a solution can only be reached if we as a society are prepared to agree with each other on how safe is safe enough. If we do not succeed in that, companies will not have a grip either to determine when and when not they should warn, with the food-allergic consumer as a victim. The knowledge and technology for a solution are available already for several years.



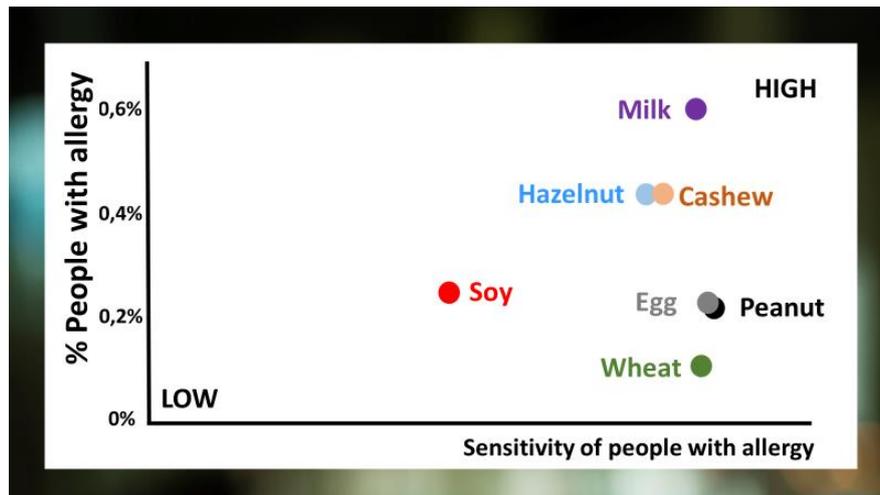
One of the first things that was needed for this was the development of a method to calculate the risks of allergens in food. TNO was the first in the world to propose and develop a method for this. We presented that idea for the first time about 20 years ago. But honestly we were a bit laughed at. The idea was nice, but to apply this method we would have to know for a large number of patients how sensitive they are to the allergens. And to that end, large numbers of patients should be given allergens to see from which dose they get an allergic reaction; to determine their threshold values. We would NEVER achieve this. Everyone knew it could not be done except me. This was in the first years of a sustainable, highly fruitful collaboration between UMC Utrecht and TNO in the field of food allergy, a collaboration that has been initiated by Prof. dr. Carla Bruijnzeel of the UMC Utrecht and Dr. André Penninks of TNO. In Carla and her colleague Dr. André Knulst, now Prof. dr. André Knulst, we found companions who also did not know that it could not be done, and they made a breakthrough by developing a good research design for this and started systematically investigating how sensitive people with food allergies are. This research was followed worldwide. Since 2010, TNO has been systematically collecting information from these types of studies by checking results from scientific publications, but also by entering into collaborations with many other hospitals around the world. A short time later, we entered into a partnership with the Food Allergy Research and Resources Program at the University of Nebraska in the United States, and we combined data from them with ours into the world's largest threshold database. This means we now know for a large number of food allergies how sensitive the patient population is to the allergens.



This allows us to calculate the risks of allergen levels in food, and, perhaps even more importantly, to calculate what the maximum allergen content may be for a maximum risk that we accept as a society. Based on our work, a guideline has been drawn up in Australia-New Zealand between 2010 and 2012 in which, based on a desired safety level agreed by all parties involved, standards for the most important allergens have been included for when and when not there should be a warning for the possible presence of these allergens. Meanwhile, more than half a decade later, we see that more and more companies worldwide and various government agencies are going to use such standards. We hope to have an update of the database ready this year and to have developed new statistical methods to be able to calculate even more precise safety limits for even more allergens. At the same time, we are in discussion with many parties and we are trying to put the subject on the agenda of the European Commission and on the globally operating Codex Alimentarius, in order to achieve an internationally harmonized and accepted standard system.

But it will take quite some years to achieve this. Wished we were as energetic as in Australia-New Zealand. When I was invited in 2010 to talk about setting up the guideline in a two-day conference in Australia, we had been talking about this in Europe already for years. During the more than 24-hour trip to Sydney I was thinking, "what can we achieve in 2 days?". But those 2 days are among the most inspiring days of my entire career so far. The first morning we discussed how the situation was at that time and we concluded that that was not acceptable. The afternoon we discussed which options for improvement there were and we chose a preferred option, after which we went to the beer. The next morning we worked out a general plan, after which we explained our ideas to the patient organization and representatives from the food sector in the afternoon. Will it be perfect? No. Is it an improvement? Yes. Then we do not wait, but we will do it, with which everyone agreed. We could go to the beer again. We went home with some homework and about a year later the guidance was a fact. We can learn something from this. In Europe too, national governments, companies and patients have a great need for clear rules on allergen labeling in food, and we see that, due to the failure of European regulators to take the lead in this, a number of national governments themselves are drawing up and implementing rules. Each, however, in a slightly different way, which only adds to the confusion. The failure of European regulators to legislate this in the EU puts more than 20 million people in Europe daily for unnecessary risks. I will continue to work to ensure that we achieve uniform rules and that in this way we will better protect the health of the food allergy patient and improve their quality of life. I know it can be done. The method to quantify the risks of allergen in food that we have devised is now seen internationally as the best approach for this problem and in recent years, under leadership of TNO, an international team has been working in a work package of the iFAAM project, co-financed by the European Union, on making this method available to companies.

Information about the sensitivity of food allergy patients to different allergens as I have left you on the screen can also be used for other purposes. I have told you before that there are regulations about allergenic ingredients that are intentionally processed in foodstuffs: food manufacturers have to state on labels if ingredients from important allergenic sources have been incorporated into a product. In principle, any food that contains proteins can cause allergies, but it is impracticable to draw up and comply with such rules for all possible allergens. That is why in all regions of the world where such legislation has been introduced, it is decided to apply it only to the most important allergenic sources. However, until recently there were no objective criteria to determine which allergen sources are the most important and the choices were therefore often influenced by political considerations. In order to make this type of choice process more objective and transparent, TNO and UMC Utrecht have taken the initiative in an expert group, under the responsibility of the International Life Sciences Institute, to draw up a proposal for objective criteria.

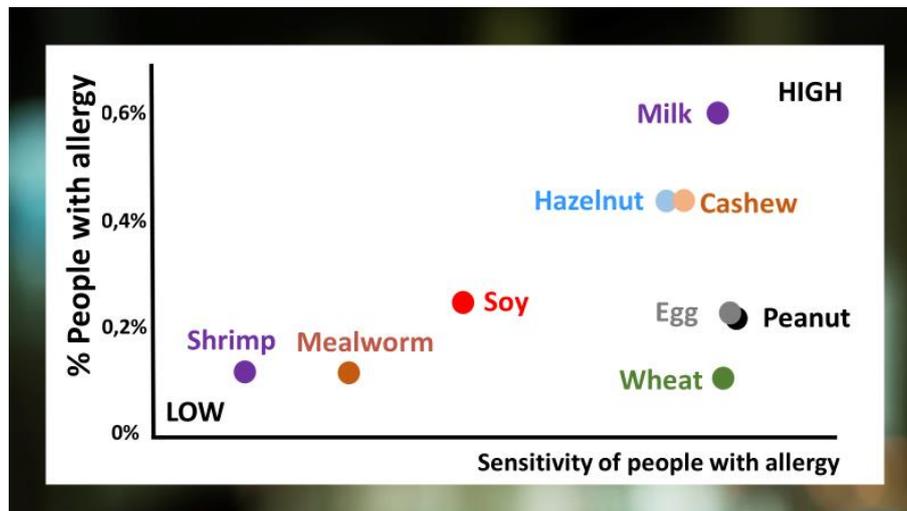


We have combined information about the sensitivity of food allergy patients with information about the number of people who are allergic to different foods and this way you can compare the public health importance of different allergenic foods. This can help make more objective and transparent decisions as to which allergenic foods should have priority for legal rules and which have a relatively small impact and need not be regulated. With efforts as set out above, we try to map out risk factors in food and make this knowledge applicable to food allergy patients and thereby help to protect the health of the food allergy patient. I am pleased with the enormous effort of my colleague Marty Blom, who works at UMC Utrecht alongside TNO and who coordinates this theme within TNO and helps me realize this goal.

I've talked so far about known allergens and risks for existing food allergy sufferers. But what we are also interested in is the development of food allergies and risk factors for this. Why do people become allergic to some foods and hardly or not to others? And why do people only become allergic to certain proteins in those foods, and hardly or not to all other proteins that are also in those foods? These questions are of great importance in this era in which we must pay attention to the sustainability of our food supply. As you all know, our food supply has an enormous impact on the environment. Replacing traditional meat sources with alternative protein sources can be an important step in making our food supply more sustainable. But it is precisely proteins that cause food allergies and it is important that new protein sources for food production do not cause too many allergy problems. There are international regulations that prescribe that any health risks, including allergy risks, of new foods must be identified and assessed before new products are allowed onto the market, but there are no clear rules and methods for identifying allergy risks. This is the second major research theme that the UMC Utrecht and TNO teams are working on and I want to continue to work hard for in the coming years.

Again, it is impossible to exclude all risks. If we want to reduce the risk of new allergies arising from new foods to zero, we will never be able to use new protein sources. New proteins will always trigger allergies in a few people. Here, too, it is important that we as a society determine how safe is safe enough. Our work in the field of known allergens can help. The figure that I have left on screen for you gives an idea of the allergy risks of some known existing foods. This can be used to compare the expected risks of new foods with the risks of existing foods that are accepted by all of us. UMC Utrecht and TNO, with the support of the Dutch Food and Consumer Product Safety Authority, have done this for insect proteins. Insects are seen as a possible alternative source of food proteins. Insects, however, have a few proteins in the body that show a strong

resemblance to proteins in shrimp. We therefore suspected that people with a shrimp allergy are at risk of an allergic reaction if they eat insects or proteins from insects. We have shown that this is indeed the case.



I show you here how the risks of mealworm, one of the insect species that we have investigated in this respect, relate to that of a number of other known allergenic foods. Here you can also see how shrimp fits in this picture. This is work from Henrieke Hustinx-Broekman, who obtained a PhD on this work last year. The number of people who are allergic to shrimp and the number of people who may be expected to react allergically to mealworm will not differ much and this is in the low range compared to various other important allergenic foods. But it is known that people with a shrimp allergy are less sensitive than people with an allergy to these other foods. Our research has shown that this may also be expected for mealworm allergy, although the allergic people seem slightly more sensitive to mealworm proteins than to shrimp proteins. We could map this for insects because we had reason to assume that people with an existing shrimp allergy might not tolerate insects. But you can imagine that new proteins in food can also cause totally new allergies. Unfortunately, research methods are lacking to map out the latter. However, we believe that if we bring all the knowledge in the field of food allergies together, we can come up with ways to make this possible in the future. This is why TNO took the initiative a few years ago to bring together as many experts from different countries as possible to jointly discuss this issue. With financial support from the European Union and coordinated by TNO more than 300 experts from 30 different countries work together in the Cost Action Program ImpARAS for four years on the development of ideas about how risk factors for new food allergies can be detected. We are very pleased that we have also been able to get people from the European Commission and the European Food Safety Authority involved, because that means that the chances that our ideas will be accepted by governments are huge. I have great appreciation for my colleague Kitty Verhoeckx, who also works at TNO and UMC Utrecht, who leads this European program and coordinates this research theme within TNO.

For decades research has been done to understand the allergenicity of proteins, unfortunately with little success. Many people think that it is not possible, but I do not. I am convinced that the key to the question of the allergenicity of proteins is to be found in the proteins themselves. Whether someone becomes allergic is determined by various intrinsic body factors, various environmental factors and the time at which, the way in which and the circumstances in which one comes into contact with the proteins. But where one is usually allergic to, is to my firm belief,

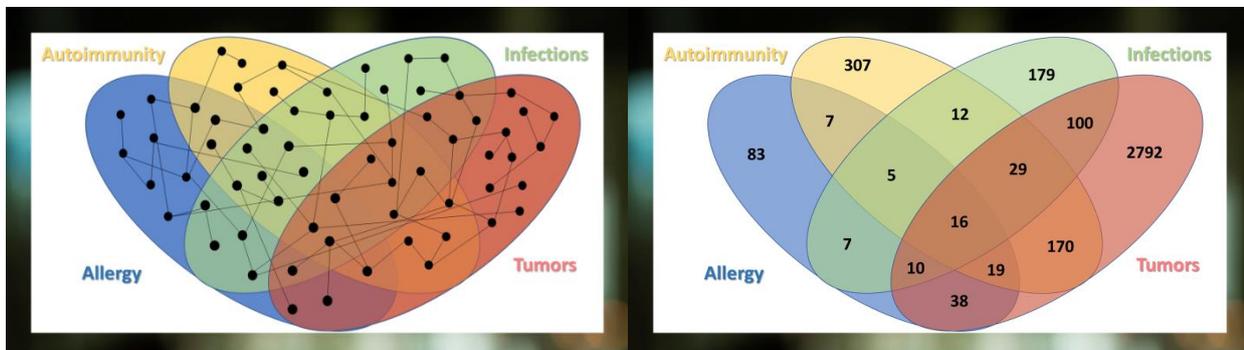
to a large extent determined by the properties of the proteins themselves. I became intrigued by this issue many years ago when, as a student, I did an internship with the late Professor Lubertus Berrens, biochemist, who led the Laboratory for Experimental Allergology at UMC Utrecht in the 1980s. I can absolutely designate Prof. Berrens as my teacher and great inspirator. In addition to passion and sharpness, he was able to recognize and bring a lot of humor into science, as witnessed by a few booklets that he produced. But he was also aware of a certain dissident place in the world of allergy researchers; it was not without reason that he chose a picture of Don Quixote on the cover of one of these booklets. He challenged widely accepted concepts, did not believe things until he had seen the evidence, and stubbornly clung to his own ideas until the opposite was proven. You understand the click between Berrens and me. We made it a game to posit contrary assumptions and challenge each other to challenge them or to prove that we could be right. He gave me the freedom to go into the lab and there myself ... well, to come up with a plan with which the technicians could go into the lab to test the assumptions. If we did not know how to get on, he would take me to a friendly professor in Nijmegen or send me to the National Herbarium in Leiden to collect evidence for or against. After my graduation until shortly before he passed away, Berrens and I often visited each other. Not infrequently, a few days or weeks later I received a package containing a book or an article from an unknown magazine of a few decades before, which addressed something what we had discussed. We regularly had an evening of philosophizing about our shared conviction that every protein is an allergen, and what an allergen actually makes a strong allergen. Berrens once uttered this, quite in imitation of George Orwell, with the quote "All allergens are equal, but some allergens are more equal than others". During my internship with Berrens, for the first time I searched through statistical analyzes in very large datasets for links that could provide indications for an answer to the question of the allergenicity of proteins. At that time, the concept of Big Data was not yet used that way, but Berrens was already working on these kinds of concepts. From this work I still draw inspiration for approaches that we work with in projects nowadays. One of the researches we are working on and appears successful is the application of machine learning methods to develop models to identify allergenic proteins. Based on dozens of properties of hundreds of thousands of proteins, including allergenic and non-allergenic proteins, these models are targeted to pinpoint the allergenic ones. Very important is research as was done by Mark Blankestijn, who received his PhD last year, who, among other things, mapped out the role of various proteins in nut allergies, and Mark Smits, who started his PhD research last year, and investigates the allergenicity of various legume proteins. I think that within a few years we will learn to read the "MESSAGE IN A BOTTLE" of allergenicity better.

The research into the allergenicity of proteins aims to understand why people react to proteins in certain ways and to help prevent new allergies for new foods. But our ultimate goal is of course to cure allergies and, preferably, to prevent people from becoming allergic at all. This brings me to the third research theme that I want to reflect on today, and here I do not want to limit myself to allergies.

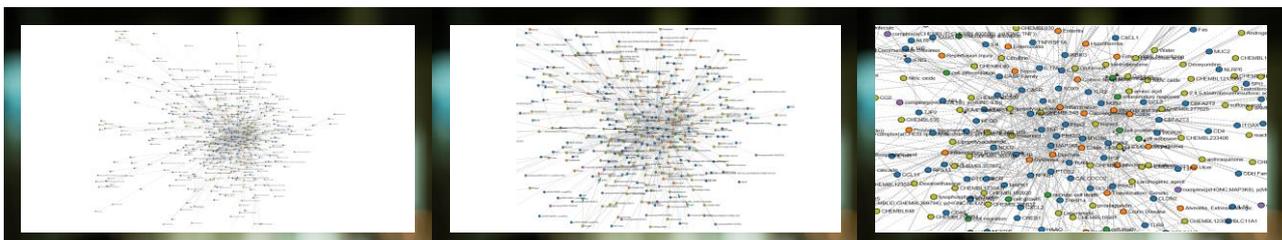
I have told you before about the major role of inflammatory processes and the impact of inflammation-related diseases. It is very important that we learn to prevent and cure inflammatory diseases better. We will have to intervene in the functioning of the immune system, in the complex structure of balances. It is likely that if we influence immune functions involved in one inflammatory disease, other immune functions also change. Of course, we do not want to

cause immune disruptions that pose different, new or bigger problems than those that we solve. For this third theme, the entire immune system, with all its roles and balances, must be taken into account in safeguarding and restoring our health. I would therefore like to call this third theme the theme of Immune Health.

The balances and functions of our immune system are controlled by a complex network of substances and molecules in our body fluids and in and on our cells and tissue, and by reactions and interactions between these substances and molecules. There is a whole network that is involved in allergies, which I symbolically illustrate with this figure. There is also a whole network involved in autoimmune diseases, and this network overlaps to a large extent, but not completely with that of allergies. The same applies to a network involved in infections, and that involved in tumors. The presence and absence and quantities of these substances and molecules are regulated to a large extent through the activity of our genes. We have looked in the scientific literature and databases which genes of the immune system are involved in allergies and autoimmune diseases or the resistance to infections and tumors, and I show you results here.



This is work of a team of my colleague Jolanda van Bilsen, who is leading this immune-health work within TNO and helps me to make our beautiful visions of the future in the field of Immune Health into a reality. You see here that, just like the networks of substances and molecules, the genes partly overlap, but that there are also genes that are only involved in three, two or one area. In future, by mapping the immune system in this way, we will better understand how the network of substances and molecules and the reactions and interactions between them regulate the functions of and balances in the immune system. Me, and with me I think many colleagues from my and later generations, know the Biochemical Pathways Poster, an immense poster of 1 by 2 meters on which all main substances and reactions and interactions of biochemical processes are represented. Until the 1950s it was inconceivable that we could ever map out the coherence in biochemical processes. We are currently in the 50's for immunology and can have an Immune Pathways Network model within a decade or two. I know we can. That is why we started collecting pieces for this puzzle and laying the puzzle in our Immune Health program. Here you see a computer view, made by my colleague Mariël van Stee, of the Immune Pathways Network as we are mapping it.



We then must, however, not consider separately the various immunological diseases and diseases in which the immune system plays a role. The mechanisms that play a role in various immune-related disorders, and particularly in inflammatory diseases, show an enormous overlap; perhaps there is more overlap than that there are differences, differences which perhaps explain the expression in various different diseases, but which often arise from imbalances in the same parts of the system. I therefore consider it very important that Prof. dr. Erik Hack of the UMC Utrecht took the initiative to call for the establishment of a Dutch Center for Immune Health. By mapping knowledge and research data from the different University Medical Centers and knowledge institutions in the Netherlands and from various immune diseases into one large database and mapping differences and similarities between the various immune-mediated disorders, we can map the Immune Pathways, develop generic immune-health-promoting strategies, and identify targets for disease-specific therapies. This can be achieved more quickly if we combine forces. With such a Shared Research we have been active in recent years. Together with my aforementioned colleagues and Marcel van Zandvoort, who met with patience for all the necessary contracts, I set up a Shared Research Program Food Allergy. In this we bring knowledge, facilities and financial resources from 15 companies and research institutions together to tackle some major challenges in the area of food allergy. Thanks in part to the fantastic project management of Astrid Kruizinga, we have already achieved a number of important milestones within the first 2 years of this program. Meanwhile, we have extended the program to a broader immune health domain. So far, we have managed to bring together a budget of 5.2 million euros and we hope to be able to add a number of new partners and at least 2 to 2 ½ million euros of new research budget between now and the end of next year. My dream is to develop such a collaboration and to make it part of a larger Utrecht program with possibly joint research facilities shared by, among others, the Utrecht University, UMC Utrecht, De Hogeschool Utrecht, TNO, RIVM and companies. Real shared research in a Joint Innovation Center. How beautiful it would be if that were part of a Dutch Center for Immune Health.

Our ultimate goal is to cure inflammatory diseases and, preferably, to prevent people from getting inflammatory diseases at all. In addition to understanding the immune system, we will also have to learn more about how we can safely influence the immune system, ... about which factors play a role in the development of inflammatory diseases and how we can influence these. In doing so, we must carefully consider the different stages of development and the dynamics of the immune system. Can we keep the immune system in check with short interventions at any time, or do we need to keep the immune system on the path of the right balance by intervening for a long time or in specific critical phases of development? For example, it is known that during the first stages of life an important basis is laid for a properly functioning immune system; the so-called "first thousand days". For years it has been the view that we can counteract the development of food allergies in children by giving children with a predisposition to allergy highly allergenic foods as late as possible. Now we know that it is possibly the other way around: by giving highly allergenic foods as early as possible, children develop tolerance and the chance of food allergy is actually smaller. Following a number of studies that have shown this, various scientists and organizations have now called for the early introduction of highly allergenic foods to be implemented as general advice. To stop a "MESSAGE IN A BOTTLE" for the immune system, so to speak. However, I am very concerned about this. Not because I think that this could not reduce the risk of food allergies. I think that is plausible. But I'm worried about safety. While everyone seems enthusiastic about the effectiveness, although in some studies and for some allergens it may be considered absent or

only limited, hardly any attention is paid to the side effects and risks that emerged in a number of studies. For example, last month at a conference in Madrid, I learned that in studies on the early introduction of chicken egg, food protein-induced enterocolitis has been identified as a possible side effect. Reducing one inflammatory disease may result in an increase in another inflammatory disease. And what happens when you introduce highly allergenic foods, while that food is not actually a regular part of the family's diet? Do you not promote the development of food allergy in such case? Maybe the benefits outweigh the risks, but in my opinion a good discussion about this is insufficiently on the agenda. The challenge is to find out if and how we can finetune the exposure of children to substances and micro-organisms via food, perhaps mainly in the first 1000 days, in such a way that we help them to develop optimal immune balance, aiming at an optimal balance between benefits and risks. So that when we put a message into the bottle of young children to send the immune system a certain direction, we do not give the wrong message, in the wrong bottle, to the wrong children at the wrong moment.

If we want to reduce the burden from inflammatory diseases, we will have to adjust or optimize the immune system from the outside. In order to make this possible and to be able to do it safely, we will first have to gain more insight into the role of risk factors that influence from externally to our immune system and how we can effectively and safely influence these factors or their effect. Through my chair I want to contribute to this by finding out how we can relate the effects of intake of thousands of substances via food, their interactions with micro-organisms in our intestines, their conversion in the intestines and their absorption into the body with the development and course of allergies and other inflammatory diseases. This may sound like a mission impossible, but let's not think that it cannot be done. Just like the challenge of mapping the Immune Pathways network, we are at the eve, or the evening has actually started, that new data analysis methods such as self-learning algorithms, machine learning, can help us identify connections between large numbers of data. I told you earlier that we have achieved success here in the search for properties of proteins that are predictive of allergenicity. I would like to examine with experts in the field of this type of methods how we can use this more broadly to better understand the interactions between food and the immune system and to find new leads for interventions. I know it can be done.

Ladies and gentlemen, I am enormously honored and grateful for the chair that has been set up and that I have been given the opportunity to execute this. I would like to thank the Executive Board of Utrecht University, the Executive Board of UMC Utrecht, the Executive Board of TNO, and all the management and staff members involved, for the opportunity offered and the trust in me. I will continue to dedicate myself to the cooperation between our organizations and the chair entrusted to me. I would like to address a special word of thanks to André Knulst, for the years of fine cooperation and mutual trust. To Carla Bruijnzeel, for the initiative, for handing over the pencil and paper and her help in putting the idea for the chair on paper. And to Erik Hack, for the watertight packaging and throwing the message of the chair in the right flow towards the Executive Board of UMC Utrecht. I would never have achieved this without the efforts of my team members and colleagues at TNO, UMC Utrecht, Utrecht University and many cooperation partners. I want to thank you all, without mentioning everyone by name, but therefore also without forgetting someone, for the fine cooperation and collegiality. I also thank my parents-in-

law, Piet and Riek, and Hannie and Fred, for the warm welcome in their family. I am very happy that Piet can be here at the age of 95. It is a pity that Riek's health didn't allow her presence.

Ton, Annemieke, Wilma, Piet and Marianne; your attention for your little brother, including your corrections and teasing, helped me become who I am and help me achieve what I have achieved. This also applies to your partners, Annelies, Leon, Fred, Mariet and Rob, most of whom were already with our family when I was a little boy. Thank you for that, and for the warmth we still experience every day. And then my parents. Mom, ... you and Dad have given me the safest home you could wish for as a child and have motivated me to learn and study, until my self-motivation had come to development by discovering my interest and talent for science. But even after that you have always supported and encouraged me. It is a pity that Dad cannot be here this day, but I am sure he would love to get up from his grave to personally push my letter of appointment under the nose of Mr. Schmeits. For those not familiar, Mr. Schmeits was my teacher in the final year of primary school, who gave me a MAVO advice. I would never get HAVO. In connection with this, I owe a big thanks to my brother Piet. Because to him perhaps I thank the most that I am here today. He was the one who strongly opposed this MAVO advice and I thank him the most that I could go to the VWO and a long detour, or perhaps a dead-end road has been saved. Finally: Gerdy, Lieke, Akke and Tessel, my dear partner and children. In the word of thanks for my PhD thesis I wrote that my family was my main motive to go to my work WITH FUN in the morning, but of course especially to go home with even more pleasure in the evenings. Now, more than a quarter of a century later, this is still the case, and our family is also enriched with the joining of Joost and Elena. Joost and Elena, I am really very happy that you have joined our family and are here to celebrate my inauguration with us. I suggest that we have a drink together on this.

I have said.

Food-borne risk factors for allergic and inflammatory diseases

***“Everybody knew that it could not be done,
until somebody came who didn't know that”***

Epictetus, AD 50-135