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From parasitism to mutualism

LEIDEN ASIA YEAR

From parasitism to mutualism

Dies lecture given by

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Why do I, a parasitologist, stand here on the anniversary of our university dedicated to Asia? Why is Asia, and Indonesia in particular, important to me, important to all of us? I would like to address these questions by using a metaphor: *from parasitism to mutualism.*

Parasitism and mutualism are all about types of dependency. The definition of a parasite is "an organism that benefits at the expense of another, the host". Parasites live in or on humans and obtain their nourishment from us to allow them to grow and to reproduce. Parasites of humans vary in complexity, shape and size, ranging from a microscopic 1 μm (blood stage malaria parasites) to up to 30 metres (the tape worm).

We get parasites via bites from flies and mosquitoes, from infested water, from the food we eat or from contaminated soil. As parasites are not predators, they do not actually intend to kill, and most parasitic infections are clinically silent. However, some can and do cause severe clinical disease and even death – such as the malaria parasite, a major killer of children under the age of 5 years, or trypanosomes that cause sleeping sickness. Even those parasites that are not major killers, when present in large numbers within their human host, lead to morbidities such as anaemia, growth retardation, disfigurement or blindness.

Parasitic infections are highly prevalent in many parts of the world, particularly in tropical areas. Three of the four most populous countries in the world are in Asia: China, with the largest population, India second, the USA (that is not in Asia) third, and the fourth is Indonesia. With its large population, Asia is not only interesting in terms of its economic potential, but also in terms of parasitic infections: the largest number of people infected with parasites live in Asia, more than 600 million people.[1,2]

Although we have worked on parasitic infections in Siberia and in India, both of which are in Asia, I would like to talk about our relationship with Indonesia. Indonesia is very close to my heart, not because I have any genetic material from Indonesia (although my genes are 100% Asian), but because I have collaborated

with Indonesian scientists for more than 25 years now and together, in equal partnership and mutual respect, we have made exciting discoveries (to be found in theses of 5 Indonesian PhD students who have already graduated and that of 4 who are at various stages of their PhD program).

Classically, parasites are considered to be bad for you; in colloquial language, the word parasite is used to indicate an undesirable guest, a useless being that lives off our riches. That we need to wipe out the killer disease malaria or combat heavy burdens of worms, to improve health in Asia, is clear. We have drugs that are very effective against malaria or worms. In fact, the 2015 Nobel Prize for Medicine and Physiology went to researchers who developed drugs against parasites: William C. Campbell and Satoshi mura, for their discovery of Avermectin, effective against parasitic worms, especially those that cause blindness, and Youyou Tu for the discovery of Artemisinin, which has saved the lives of many people with malaria.[3] However, although these drugs are effective as cures, they do not aid prevention. A child can take a drug today that kills its parasite but the very next day that same child can acquire a new infection from an infected mosquito or from contaminated food or soil. Re-infection means that current global efforts towards parasite elimination that entail drug treatment only will not work.[4-7] Elimination is only possible in combination with prevention, and one of the most effective means of prevention is to develop a successful vaccine and combine this with health education. At LUMC we developed the first genetically manipulated malaria parasites 20 years ago.[8] These parasites are so weakened that they cannot cause disease but induce a strong immune response and therefore can act as a vaccine.[9] In a fierce race against the clock, our Dutch vaccine will enter clinical testing this year. We are also among the international teams working on the development of vaccines against schistosomiasis and hookworm infections, caused by the two most important parasitic worms.

Colleagues across Germany, the UK, the US, Australia and the Netherlands have developed innovative ways to cut time and costs in vaccine development by initiating controlled human infections, whereby with the utmost consideration for safety (a radical cure for the infections must be available), healthy volunteers are

infected with a number of pathogens, among them malaria and parasitic worms.[10] This allows candidate vaccines and drugs to be tested rapidly to allow the most promising ones to enter large-scale trials, among others in Asia.

However, there is another story as well, that we may need to consider parasites in a more favourable light. With increasing scientific research we have gained insight into some beneficial effects that some parasites seem to have on their human host. In areas where parasitic worms are highly prevalent, there is little evidence of allergic diseases even though there is great exposure to allergens such as the house dust mite, pollen or peanuts. Whereas 1 in 4 children in the Netherlands suffers from allergy-related disorders[11], in rural Indonesia, on Flores island, in the village of Nangapanda, this number is much smaller, around 1 in 10.[12] The question of whether worms can have beneficial effects was addressed by infecting mice with worms and showing that infected mice developed far fewer allergies compared to uninfected ones[13,14], confirming that parasitic worms might also have some beneficial effects. How does that work? How can a parasite suppress allergy-related diseases?

It does so by manipulating the immune system. You have to realise that we are dealing with special organisms; they are not like the simple poxvirus that kills its host. No, parasites are sophisticated with a large genome that is endowed with a great capacity to allow itself and its host to survive. The parasitic worm has the ability to change our immune system in such a way that the immune system cannot attack it, which means the parasite is able to survive for years. You could say that we in effect tolerate the unwanted organism.[15] When a person infected with parasitic worms, is exposed to allergens, for example to pollen or house dust mite, there is no aggressive reaction to the allergen, so unlike people who react fiercely to allergens and develop allergic diseases, in parasite-infected subjects, the allergen is tolerated[16,17] and consequently there is less chance of developing an allergic disease. More recently, scientists from Stanford University have shown that the manipulated immune system that is induced by parasites is important for glucose metabolism, for our ability to control glucose levels.[18] If we fail to control our glucose levels, allowing them to rise, we become sick; we develop diabetes.

One form of diabetes is when our body is resistant to the working of insulin, an important hormone that controls glucose levels. Experiments in animal models have shown that mice infected with parasitic worms are less likely to develop Type 2 diabetes or insulin resistance.[19] Together with Indonesian colleagues, we have looked at this in humans. Work on Flores Island has shown the population there to have a much healthier glucose metabolism compared to people from Flores island who live in Jakarta, the capital city. This seems to have something to do with parasitic infections prevalent on Flores Island. The team found that subjects on Flores island infected with parasitic worms had less insulin resistance than those who were not infected, and that an increasing number of parasitic worms went hand in hand with increasing improvement in insulin sensitivity.[20] A very recent clinical trial showed that treating the parasitic worms resulted in an incremental, but significant, increase in insulin resistance.[21]

This becomes really interesting. If, instead of using live worms to avoid the detrimental consequences of parasitism, we take certain molecules from worms and inject them into animal models, we find injected animals are less likely to develop Type 2 diabetes.[19,22] There are now quite a number of molecules derived from parasitic helminths that are able to suppress diseases such as allergies, diabetes or other inflammation-driven conditions.[23]

These studies indicate that we should really move from the outdated way of thinking regarding parasitism to what is considered as mutualism. Mutualism is a term that indicates a relationship where both organisms benefit from each other: together they are better. Parasites use our food and they manipulate our immune system to allow their survival in our body, but there is also some degree of mutualism as we can also benefit from parasites: our altered immune system means we develop fewer of the diseases that are rampant in areas where parasites no longer exist.

From parasitism to mutualism; does this mean we are going to leave people infected or treat patients suffering from allergies and diabetes with worms? I doubt we would want to do that, even though patients call begging to be treated

with worms having heard of their possible beneficial effects. No, but with our top-level sophisticated technological platforms and scientific tools we can dissect how these parasites exert their effects, identify the battery of molecules and manipulate them such that we can target the immune system very specifically to make us less susceptible to disease processes, to allergies, to diabetes and maybe to other inflammation-driven disorders.

The shaping of the relationship between the Netherlands and Indonesia offers unprecedented insights and opportunities, for both countries. In the context of "*From parasitism to mutualism*", let us reflect on the relationship between the Netherlands and Indonesia. Up to 1870, the relationship could be considered something approaching parasitism, when the Dutch were benefiting from Indonesia. After that, dependencies evolved where the Dutch started to invest in education and welfare. The establishment of modern development aid ushered in a period when Indonesia could be considered more dependent on the Netherlands. Where we stand now is that Indonesia, a lower-middle income country, is entering a new relationship with the Netherlands: it is considered as a so-called transitional partner country. This means that the programme for development cooperation will gradually be phased out and replaced by a stronger focus on economic cooperation: from aid to trade.[24] There will a shift from the historical, one-way dependency to mutualism, where the dependencies will be based on mature equal partnerships that benefit both countries.

Within this framework, we can create new opportunities to work together in higher education, research and innovation – factors that lie at the very root of successful long-term trade, with the emphasis on 'long-term'.

Indonesia, with its more than 10,000 islands spread over around 2M square kilometers, represents one of the most diverse countries in the world. Although one of the most promising countries economically, huge differences are masked, with many islands that are in dire need of development. Disease patterns are extremely polarised, whereby a large proportion of the population in rural areas suffer from parasitic and other infectious diseases, while the rich in large urban

centres, face diabetes, and cardiovascular and allergic diseases. In the 1930s, only 5% of the Indonesian population lived in cities; in 1960 this number was 14.8%, and in 2015 54%.[25,26] With the increasing urbanization of Indonesia, there is also a rapid transition in lifestyle and environmental factors. We see a close link between these changes and the changes in disease patterns, many of which can also be ascribed to alterations in metabolism and immunological processes in the body. In some rural areas of Indonesia, living conditions are similar to the situation in Europe or the US more than 100 years ago, whereas for the rich in its urban centres their living conditions equal or surpass those found in European or American metropolitan centres. This gives us the opportunity to understand how the changes in the environment over the past hundred years have affected our metabolism or our immune system and thereby our disease patterns. Understanding this is key to preventing disease. In a sense, Indonesia is driving in the fast lane; it is an exciting, rapidly evolving country where Indonesian and Dutch institutions can work together to harness infectious diseases through developing new drugs or vaccines, and at the same time dissect the processes that are leading to the emergence of modern diseases. With the contribution from our universities, our top-level technological platforms and our highly trained workforce, we can shape the future health profile of our countries. Europe is facing an epidemic of modern diseases, and Indonesia will follow suit if we do not find ways to combat these diseases. Needless to say, such a programme can be successful only if we work in interdisciplinary teams where not only our medical faculty but also our science, social sciences, humanities and law faculties, among others, work together to provide the broad knowledge base needed.

Why should the Netherlands and Indonesia work together? The history, although at times bitter, also has its positive aspects that need to be acknowledged: these include a thorough understanding of each other's cultures, living environments and scientific interests. Familiarity is an essential step that will give a powerful advantage to both countries. Our strong higher education system and highly innovative technology sector are of great interest to Indonesia. On the other hand, Indonesia, with its diversity in culture and religion, has a tradition of tolerance. In parallel, biologically, I just mentioned that Indonesians have a more tolerant

immune system and are therefore less receptive to developing many modern diseases (especially in rural areas). We need to learn from them how they achieve this. In Indonesian universities, women leaders outnumber men, which usually reflects the lower salaries earned in this sector in developing countries. However, a better indicator would be the private business sector. A study by Grant Thornton[27], shows a higher percentage of female business leaders in Indonesia than in the Netherlands. Maybe it is not a coincidence that the Minangkabau, the world's largest matrilineal society, is in Indonesia?

Although, through our intertwined history, the Netherlands still has a privileged position in Indonesia, the gap is closing. It is closing with countries such as the USA and UK investing in higher education and innovation. Why is it that, whereas the USA[28] and UK[29] are increasing investment in Indonesia in higher education and research, the Netherlands is backtracking[i]? The SPIN programmes of the KNAW, the special funding schemes for research and innovation that were reserved specifically for partnering with Indonesia – that many of my colleagues abroad were very envious of – why are these programmes ending or no longer there? We have over the years trained Indonesian scientists and medical staff here at the LUMC, who later return to their home country. While Indonesia accommodates them, giving them seed funding, they still need their international relations to thrive. Currently we are losing them to our competitors who have the long-term vision of investing in the future of their link with Indonesia, a country that is increasing its focus on higher education and research.[30] With a sense of urgency, let us in the Netherlands strengthen our collaborative bilateral programmes between Indonesia and the Netherlands, and plan a long-term vision beyond the current aim of 'from aid to trade', that accommodates higher education, research and innovation.

During a period of increasing nationalism, internationalisation can be in danger. International students add to the research landscape a richness and diversity not otherwise possible in a country as small as the Netherlands. We would do well to remember that international students from Asia will foster the future friendship between our countries. Internationalisation should be cherished by academic

centres; such centres can play a role in our society to continue working with culturally distinct countries. Nationalist political events such as Brexit or Trump's election are expected to result in a fall in the recruitment of international students by the UK and the US, which are traditionally leading countries in terms of international student exchange. This could create opportunities for other countries, including the Netherlands.

Leiden University has at its heart internationalisation. At the LUMC, where patient care means that the Dutch language dominates medical education, we have put much effort into developing English modules within the curriculum to create an international classroom and to provide international students with the opportunity to gain exposure to our University. One of the examples is the half-minor/elective programme. While our students have been welcomed by our Indonesian colleagues in Indonesia, increasing numbers of Indonesian students have been coming to LUMC to get the best education from top researchers and clinical professors. This has been an amazing experience and is highly appreciated by the students. I would like to quote from one of these students:

"Dear Prof Maria

Vito & I have arrived safely in Jakarta. Thank you for the opportunity to join (the Heart and Blood vessels programme, one of the 15 half minors). Ten weeks during the minor have opened my eyes about various novel things in the field of cardiology and vascular medicine ... This minor convinced me that the medical world is constantly changing, research continues to be developed, and what we believe now may not be the truth. As one said, half of what we have learned is wrong, and half of it is right; the problem is that we don't know which half is which.

My interaction with classmates and the doctors in LUMC also opened my eyes to how medical education in the Netherlands works, encouraging students to think and appraise critically and to be exposed to research and scientific articles as early as possible.

Research in Indonesia is still something that is quite underestimated and underdeveloped, despite the enormous potential as a tropical country with quite a high population. I wish I could bring a change in the future, and the experience in this minor surely will be a great foundation for that."

LUMC, alongside Leiden University's historic and current strong ties with Indonesia, supports the exchange of undergraduate students, PhDs and scientific as well as clinical staff. This is a reflection of the appreciation of the opportunities that lie ahead in higher education and research for both countries. I am hopeful that this will set the example for mutualism whereby our two countries form a partnership in which commitment from and benefit to both sides will be key. I hope this will lead to mechanisms for the long-term propagation of excellence together, an essential pre-requisite to tackling our societies' pressing problems.

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* In the period 1994-2004 the subsidy from OCW for scientific cooperation was € 22.523.381 (in addition for administration the subsidy was € 68.067 per year in this period). For the period 2005-2017 the overall maximum subsidy will be maximum of € 15.735.000. A decline in the funding for Indonesian StuNed (Studeren in Nederland) program is seen: approximately € 6.000.000 per year in 2005-2009. Again € 6.000.000 per year in 2010-2014, but this dropped to € 2.600.000 per year for 2016-2018.
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Maria Yazdanbakhsh (1959) studied at London University and obtained a Master's in Medical Parasitology from the London School of Hygiene and Tropical Medicine. During her PhD at the University of Amsterdam, she combined immunology and parasitology and was subsequently granted an EU scholarship for post-doctoral research in molecular parasitology at Imperial College in London. She started as a lecturer at the Medical Faculty of Leiden University and now heads the department of Parasitology. This department combines basic and clinical research and employs an interdisciplinary group of basic and clinical scientists who focus on understanding host-parasite interactions at molecular, cellular and population level. Maria Yazdanbakhsh specialises in combining field studies in South East Asia and Africa with molecular immunological work in Leiden. The knowledge gained from these studies is being applied in two ways: 1) to develop effective vaccines against parasitic diseases, and 2) to identify parasite-derived molecules to control diseases such as asthma or type 2 diabetes. She has contributed to (bio)medical education by coordinating the development of 15 LUMC half-minors/electives (lumc.nl/onderwijs/international-students/electives/), which are also offered to international students, and has supervised some 27 PhD students. She is the president of the Dutch Society for Parasitology and holds a visiting professorship at the University of Indonesia in Jakarta.