NWO

# Eminent Talent

## 2008 – The fourtheenth year

Netherlands Organisation for Scientific Research

**Prof. M.S. (Marjo) van der Knaap (1958), paediatric neurologist at the VU University Amsterdam.**

Van der Knaap is an internationally recognised authority, who pushes back the frontiers of her discipline and pursues a disease from cause to cure. She works across the entire spectrum of clinical practice from contact with the family of the young patients to identifying new variants of the disease.

# Like a detective searching for the genetic culprit

White matter disorders are diseases affecting the white matter of the brain. They can give rise to severe motor problems. With the help of MRI scans, paediatric neurologist Marjo van der Knaap has diagnosed several of these rare diseases and tracked them down to the level of the responsible genes.

The first white matter disease which she unravelled has a difficult name: megalencephalic leukoencephalopathy with subcortical cysts (MLC). Children with MLC most often have consanguineous parents, frequently full cousins. 'If both parents carry a gene with a defect and they have children together, then such rare disorders suddenly surface. The probability that both parents are carriers of a rare gene defect is, of course, greater if the parents are related', says Van der Knaap. 'During the first year of life, children with MLC acquire a large head, similar to children with hydrocephalus. When an MRI scan of such a patient is made, the white matter disease is right in your face.' After a few years motor problems usually become manifest; as teenagers the majority of patients become wheelchair bound. Most patients do not die until adulthood, after years of increasing handicap.

The heart of the problem lies in damage to the millions of long nerve fibres in the middle of the brain. They are surrounded by myelin, a white substance, which ensures that the conduction velocity of nerve fibres, the connective pathways, becomes extremely fast. If the transmission of nerve signals becomes deranged, messages can no longer be correctly transmitted to the body. 'At a cognitive level the patient remains relatively intact, but the body no longer obeys', explains Van der Knaap.

## Swelling

With an overall frequency of one in one thousand children, white matter diseases are rare conditions in the Western world. Yet that has not prevented her from completely devoting herself to this phenomenon ever since her doctoral research. Not for career reasons but mainly because medics were at a complete loss on the subject of white matter disorders up until then. 'I like solving puzzles and neurology is about solving puzzles in all aspects', says Van der Knaap. 'The fact that white matter diseases are rare, only made it more challenging. I immediately saw that it must be possible to recognise these conditions on the basis of MRI patterns. And that proved to be the case.'

Van der Knaap developed a computer-guided MRI pattern recognition system that enabled her to establish diagnoses in a faster and cheaper manner. In the case of MLC, the first new white matter disease she managed to describe on the basis of pattern recognition, it became clear that the swelling of the baby's head was caused by countless fluid-filled vesicles in the white matter. Internationally this is now referred to as 'Van der Knaap disease'. A great honour or not? Van der Knaap: 'No! It is not a good idea to name diseases after people! Furthermore from an international perspective I have anything but a simple name. I wrote a letter to the journal that first used the name to protest against this.'

The next stage was identifying and describing the genes responsible for the disease. The hunt for the gene not only proved successful in the case of MLC, but also in the case of the second white matter disease she described: Vanishing White Matter (VWM), a disease in which the white matter of the brain disappears. The effort required for this had the character of a genuine 'whodunnit'. Van der Knaap and her colleagues discovered that one of the epidemiological foci of this disease was located in the area around the Dutch town of Zwolle. She specifically targeted the research on that area. That soon proved to be crucial because genealogical studies demonstrated that the six affected families she had selected shared a common ancestor, who lived in the vicinity of Zwolle in about 1800. A mutated house-keeping gene was found to cause a defect in the synthesis of proteins and in the regulation of protein synthesis. Especially in the event of stress or fever, when the production of proteins should decrease, these patients deteriorate neurologically. 'In this case the problem does not lie in the marrying of cousins; a relationship that goes back centuries can be fatal as well', says Van der Knaap. 'The discovery of the genes for vanishing white matter was major news and the world of protein synthesis was briefly shaken.'

## Mouse model

With a record of five 'solved' white matter diseases, Van der Knaap is now considered to be an international authority. Each year she receives about 800 MRI scans from throughout the world for a second opinion. She solves a substantial percentage of these and the international networks that she builds with these second opinions in turn provide a wealth of new information. Many of the Dutch white matter patients end up at her research centre at the VU University Amsterdam. Unfortunately this often results in 'bad news' consultations. Doesn't that bother you? 'No. Although patients still die, we can now help families with prenatal diagnosis and carrier testing. Information is also extremely important: we make it possible for parents to see their child's killer in the face. The pain of parents who do not know what their child has died from is worse.'

Research into treatment methods is now proceeding apace for several white matter disorders. In each case the treatment is tailored to what is known about the function of the gene concerned. Van der Knaap is currently working on a mouse model for Vanishing White Matter. The starting point is that early stem cell transplantation could be an effective treatment for VWM and that this must be trialled. For MLC she is searching for drugs to combat the unwanted accumulation of fluid within brain tissue. 'We might be able to save these children if we could remove the water from the brain at an early stage', hopes Van der Knaap. Seeing so many children in her work that are gravely ill and eventually die, does not deter her. 'Children are fantastic. They do not complain; they too only get one life and have to make the most of it. They're happy with the smallest things. That motivates me. Moreover, the diseases are very rare and are complicated. They are the difficult puzzles. Solving these is my passion.'

**Prof. J.Th. (Joep) Leerssen (1955), professor of Modern European Literature at the Universiteit van Amsterdam.** Leerssen's unique profile has enabled him to develop an impressive interdisciplinary method for this discipline. This approach combines the history of political ideas with the history of culture, and uses literary sources to investigate the history of imagology and ideologies.

**Prof. J.Th. (Joep) Leerssen**

# ‘Nationality is not a question of being but of seeing’

Princess Máxima recently unleashed a storm of protest with her observation that the Dutch identity does not exist. Critics accused the Princess of ‘politically correct claptrap’ and a row erupted. Professor of literature Joep Leerssen, specialist in the area of national stereotypes, followed the discussion with amazement.

‘What Máxima said was absolutely true, she merely stated the obvious’, exclaims Leerssen. ‘The Dutch identity is – just like every other national identity – a lucky dip. Who then is typically Dutch? The popular crooner Gordon, Queen Wilhelmina, Paddeltje (character from a 19th-century boys’ classic), the anti-Nazi Resistance heroine Hannie Schaft, legendary football trainer Rinus Michels, my mother? People select whatever they have a need for at that moment in time.’

National identity is – just like all imaging – always contrastive and its aim is to define boundaries and distinctions, explains Leerssen. Dutchness is formulated to indicate the contrast with, for example, the Germans. That is realised by the creation of Dutch and German stereotypes. Yet this only makes the phenomenon more interesting to him. Leerssen, one of the founding fathers of the discipline European Studies, has acquired an extensive knowledge of national stereotypes and imaging. In his recent publications National Thought in Europe: A Cultural History (2006) and Imagology (2007) he describes the history of these using literary sources. In the European patchwork quilt of countries and peoples, imaging and stereotypes appear to play an important role, with a particularly distinct characterisation at locations where different identities come into conflict. He discovered that, for example, in his ‘second fatherland’ Ireland, where he lived for a period during his PhD studies, met his wife, in passing completed a course at a music academy and worked as a professional flautist for another two years.

Irish sources from the 17th century caricature the English enemy as an unimaginative, short-sighted, stolid people with little more interest than acquiring money – an image that many other peoples have of their oppressors. English sources describe the Irish as a barbaric and cruel people, an image which was resurrected in the 20th century at the peak of the IRA violence. In the 18th century the image changed: The Irish were depicted as a romantic, innocent people of mystics and dreamers. ‘Whiskey adverts now make grateful use of that mysterious image’, chuckles Leerssen. ‘The development of such a bipolar image of a people is commonplace. In travel guides to Ireland you are sure to read the comment that it is *a country full of contrasts*. Of course that is claimed about every country.’ National identity is, says Leerssen, not a measurable behavioural pattern within a society, but revolves around identification with a certain self image: What are the terms in which a given society sees itself? Leerssen: ‘Nationality is not a question of being, but of seeing. The word identity means little in that context and so far as I am concerned it could be dropped.’

## Steak

For the same reason, the discussion about the 'multicultural society' or its failings is equally absurd in his view. 'A society is by definition multicultural – and that is not just a politically correct piety. Culture in the deepest sense of the word is a system of diversifications in behaviour, in moral opinions and in identifications. Put briefly: Culture is everything that you could also do differently. All of us physically observe the world in the same manner, in so much as the human eye sees light in a certain spectrum. From Zimbabwe to Alaska we all swallow in the same way. Culture is: producing sunglasses or lenses, or how we prepare our meal: Whether you fry the steak with onions or tenderise it under the saddle of your horse. Being able to be different is a key aspect of what culture entails. It's about the differences: in diet, accent, religion, art, et cetera.'

European Studies describes regional differences and analyses their development – and the interaction between cultural imaging and political decision-making – over the course of centuries. The emphasis is on nation-formation in the nineteenth century. That process is usually explained either as a product of political manipulation – as a side effect of modernisation – or as an embodiment and institutionalisation of an underlying ethnic entity uniting members of an ethnic group. Leerssen considers both ideas to be inadequate, 'since neither allows for the historical changeability and dynamics of culture in its impact on political attitudes'. He argues that nationalism must be studied as a cultural political agenda, from the image that inhabitants of a region have of themselves and from a historical perspective. If you want to get to the heart of the nationality problem then an integrated and comparatist approach is indispensable. The manner in which Leerssen made a name for himself in the area of Irish studies illustrates this. In literary studies, Irish literature was always considered as either a branch of Celtic studies, or as an outrider of the English cultural sphere. And that is an inadequate approach, argues Leerssen, as with this several interesting interactions fall completely out of view. He therefore made a comparative study of numerous Irish texts in English, but also Irish (Gaelic) and Latin. Leerssen: 'If you view a culture from the perspective of one language then you look through just one keyhole. It is just like the parable of the blind men who feel an elephant: One feels the trunk and says that an elephant is like that, another grabs hold of the leg or tusk and says that the animal looks completely different. I am looking for an integrated vision. Cultural relations are far more complex than the jigsaw puzzle vision that we learnt at school.'

Leerssen wants to use his NWO/Spinoza Prize for a large-scale study into European nationalism. European nationalism? Leerssen: 'Most certainly, there is a nationalism that is definitely European, despite all of the differences within that continent. Between 1780 and 1850 intellectual networks of cultural nationalists arose throughout Europe – from Iceland to Portugal to Russia – which continually exchanged ideas. National identities did not arise independently of each other, but under the influence of people who reviewed each other's books and were members of the same scholarly associations. Consequently there was a coherent Europe-wide process of national-cultural partitioning. As if cultural autism was infectious. In the case of nationalism each movement establishes and proclaims its own separate uniqueness, sometimes without realising that the very same thing occurs everywhere else as well.'

Although he will not be able to exhaustively tackle the subject in five years, Leerssen nevertheless hopes to realise a provisional main result in the form of an encyclopaedia of all important names, networks and affairs of European cultural nationalism.


**Prof. Th.H.M. (Theo) Rasing (1953), physicist at the Radboud University Nijmegen.** Rasing performs groundbreaking fundamental research with a keen eye for possible applications. His research into the manipulation of magnetism using light might ultimately lead to technology that can record information up to one hundred thousand times faster than is currently the case.

# Saving computer bits ten-thousand times faster

Recording the ones and zeros on a hard disk using an electromagnet, as in a traditional PC, could become a thing of the past. With the help of laser pulses and a splinter-thin magnetic layer recording can be performed 10,000 times faster. Experimental physicist Theo Rasing opened up new avenues for research with this discovery.

When his research group from Radboud University Nijmegen announced the discovery in 2007, it flew in the face of previous experiments from which it had been concluded that such a feat was absolutely impossible. ‘It was always claimed that switching a magnet in a time span of less than about 100 picoseconds was impossible. But of course we are always searching for ways to circumnavigate fundamental limits’, says Rasing.

Up until about 20 years ago magnetism was a ‘finished’ subject. Despite important applications such as the compass, the electromagnetic motor and the videotape, no new fundamental discoveries were being made. This all changed when experiments using ultrathin magnetic layers produced completely new effects. It even provided Albert Fert and Peter Grünberg with the Nobel Prize in Physics last year. Surprising phenomena also occurred in the dynamics of the magnet – the changing of the North to the South Pole – when for the first time ultrashort light pulses were fired at a magnet. ‘In my field it only gets interesting if you go faster than a picosecond – one millionth of one millionth of a second. And that was found to be possible with the help of light’, says Rasing, who plunged into this new research discipline as a young physicist. His first surprising result was that a very strong magnetic field pulse can be generated with the aid of light. Previously that had only been realised by means of rapid heating, a phenomenon that works far less efficiently. Rasing’s research group recently achieved another world first when they proved that a laser pulse could switch the orientation of a magnetic particle in the record time of 0.1 picosecond. ‘Spectacular of course, because when an electromagnet is used that costs about 1 nanosecond per bit’, says Rasing. ‘Yet the IT industry responded with a certain amount of scepticism, as such a technique can only be used for data storage if a magnetic particle can be rotated by a full 180° from the North to the South Pole. I immediately responded that there is no fundamental law to prevent that.’

Last year an experiment performed by the Nijmegen research group proved that Rasing was right, a finding which he patented immediately. Understandable, because the discovery could mean a quantum leap forward for computer technology. In theory at least, because the switched domains in the thin film on Rasing’s desk are no less than 5 micrometres in diameter. ‘Of course for computer applications that is enormous; the diameter will have to be reduced to just several tens of nanometres.’

**Motivation**

And so for the time being there is still plenty of work for the Institute for Molecules and Materials (IMM) of Radboud University Nijmegen. In 1997, Rasing founded the predecessor of this institute, following various posts as a researcher in Slovenia and the United States. The farmer's son from Didam, whose family always encouraged him to study further, ended up in fundamental research for one simple reason: 'This is my passion and that is the only motivation I need. You can only keep on working hard if you really enjoy what you do.' Pleasure in his work was one of the reasons why he returned from Berkeley to his home patch. In Nijmegen he was given the chance to set up his own research group in the area of non-linear optics. 'Yet now with magnetic materials. In Berkeley they did not believe in this at all.' With the institute he developed a method to render molecular motion visible using laser pulses and he carried out countless experiments with ultrathin magnetic layers.'

Rasing is visibly happy that so much has been achieved in such a short time. 'We have demonstrated our ability to build a top institute.' The IMM has quickly developed into a bustling institute, with an attractive new building and a rapidly growing number of students, researchers and spin-off companies. In the research laboratories, Rasing has advanced lasers and vacuum equipment at his disposal. Technicians in the new High Field Magnet Laboratory (HFML) are currently building an electromagnet with a stationary magnetic field of 45 Tesla. Moreover, right next to the HFML a start will soon be made on the construction of a Free Electron Laser for research into biomolecules and materials in high magnetic fields. Rasing is extremely proud of this. 'With these initiatives we are setting the pace in Europe.'

**Back door**

The recent discovery of the method to save bits using laser pulses is the main focus of the IMM researchers at present. Rasing intends to use part of his NWO/Spinoza Award for cracking the fundamental problems that will be encountered in converting the discovery into an application for the computer industry. With these efforts he will also come up against the boundaries of the laws of physics. 'Sometimes you have to find a back door', says Rasing. 'That is how we achieved this first spectacular step as well. However, that was so unexpected that we are still missing a microscopic support for this. We are not entirely sure ourselves yet if our explanation for this phenomenon is correct. Therefore over the coming years we not only want to formulate the next steps, but also increase our understanding of the discovery. This is particularly important because the potential application area of light manipulation of magnets is far bigger than just the realisation of an ultrarapid computer. Advanced laser pulses can also be used, for example, for the cooling, setting into motion and stopping again of individual atoms. Accurate control at the atomic level in solids is still pretty much an uncharted research area. Rasing: 'Fundamental physics, therefore. Fantastic, because ultimately that is what drives me.'


**Prof. W.M. (Willem) de Vos (1954), microbiologist at Wageningen University.** De Vos is a pioneering researcher. His most recent breakthrough was the invention of a revolutionary 'smart petridish'. Using this he has shown that both new species and previously uncultured species can be isolated.

# No life without bacteria

The Earth is literally teeming with bacteria. An incredible $10^{30}$ bacteria populate our planet and 100,000 billion of these alone can be found in the intestines of each and every person. Microbiologist Willem de Vos explores the world of these unicellular organisms and investigates how they can benefit us.

Without a doubt bacteria are more than just pathogens. 'They might not be cute but they are vitally important', grins De Vos. 'Let me put it this way: without bacteria there would be no life on this planet.' To illustrate this, the microbiologist from Wageningen University draws a circle on a piece of paper ('this is a person') with a tube inside that represents the intestines. 'From within and without humans are covered with bacteria; we all carry about a kilo of bacteria around with us. And with this we live in a perfect symbiosis.' Some species of bacteria play an important role in the host's health, whereas other species, for example, are responsible for almost half of all photosynthesis on Earth. Photosynthesis produces life-sustaining oxygen and ensures the removal of carbon dioxide from the atmosphere – bacteria therefore play a crucial role in mitigating the greenhouse effect.

De Vos' fascination for the powerful, yet without a microscope invisible, kingdom of the bacteria can be traced back to his interest in the origin of all life on Earth. De Vos: 'Microorganisms were the first forms of life on this planet. All visible forms of life are much younger. If you look for our last common ancestor then you end up at extremophile microorganisms that can grow under the most bizarre conditions.'

Archaea are extremophiles and some species thrive at or above the normal boiling point of water. De Vos discovered that glycolysis in these species proceeded via a different pathway and with different enzymes than that described in the textbooks. 'This type of Archaea are particularly interesting microorganisms for the processing industry, as they contain enzymes that are both active and stable at high temperatures and under various inhospitable conditions.'

### Communicating bacteria

De Vos, however, mostly earned his spurs for his work on lactic acid bacteria and fermentations. His research at the Netherlands Institute for Dairy Research (now NIZO Food Research) not only resulted in cheese and other fermented dairy products with an improved taste and shelf life but also led him to several surprising scientific discoveries. For example, he discovered that lactic acid bacteria can communicate with each other in their own 'chemical language', with the help of peptides. De Vos: 'With this process, the cells are aware of each other's presence and collectively know how many of them are present. Pathogens, for example, make use of this. They want to grow in a host, but cannot realise that alone because they are easily recognised and deactivated. They must first of all form a sort of Trojan horse with each other to evade the host's immune system. What do they do? They secrete signalling molecules, such as peptides that contain just several to some dozens of amino acids. The cells recognise each other's molecules and so know how many of them are present. If the concentration is high enough, they launch a joint attack. This is, therefore, an example of behavioural coordination using signalling molecules.' The discovery of these signalling molecules and the signal transfer system, subsequently enabled De Vos to allow the bacteria to perform tasks at command and to indirectly elicit certain reactions in the cell. 'This approach allows you to direct the gene expression. Very handy for manufacturing biotechnological products.' The NICE (Nisin Induced Controlled Expression) system is now used throughout the world. De Vos used the method to force lactic acid bacteria to produce useful substances such as the amino acid alanine, flavourings and vitamins by specifically influencing the metabolism.

Another more recent discovery, which he successfully pursued and patented is the smart petridish. This contains a microchip with millions of tiny chambers in which small populations of bacteria and other microorganisms can be cultured next to each other and studied using a microscope or digital camera. This new method is quicker and cheaper than the existing method in which complete colonies had to be grown in a petridish. The 'petrichip' can also be used to search for the figurative needle in the haystack, as characteristics that are virtually impossible to find in colonies can easily be sought at an early stage.

**Routine research**

For the past few years De Vos has mainly focussed on microorganisms in the human gastrointestinal tract, the so-called intestinal microbiota. 'This mostly consists of bacteria which produce useful compounds, breakdown indigestible food components and communicate with the cells of our body – they are therefore vitally important for our health. Consequently unravelling which bacteria this microbiota contains and what the DNA looks like is big business', says De Vos. 'Recently, it became clear that deviations in the intestinal microbiota are correlated with conditions such as Crohn's disease, ulcerative colitis and irritable bowel syndrome, but also obesity. We want to render the functions of the intestine visible by examining the bacterial species present and their activity. To this end we have developed a number of smart DNA chips which can rapidly render the species richness visible.' De Vos estimates that there are some five hundred to a thousand species of intestinal bacteria in each individual person. Yet for more than eighty percent of these almost nothing is known – many of the species have never been cultured and the 'petrichip' can provide a way forward here. 'Additionally within an international consortium we are investigating possible functions by mapping and analysing the DNA sequences of the intestinal microbiota.'

In practice this means investigating bits of intestine and faecal samples. De Vos, who is a professor at the universities of Wageningen and Helsinki, carries out the research while travelling back and forth between the Netherlands and Finland. For him, Finland is the Mecca for research into intestinal microbiota because many longitudinal studies have been performed there with homogenous population groups. A lot of routine research still needs to be done and the smart DNA chips, the 'petrichip' and the NWO/Spinoza Award will greatly facilitate this process.

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