



# Rudolf Magnus Institute of Neuroscience

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## interview

### At high risk after the bubble bursts

**Aneurysms are balloon-like abnormalities in blood vessels. When such an aneurysm, existing in a vessel within the skull, ruptures a subarachnoid haemorrhage (SAH) occurs, with a chance of survival of only 50%. As aneurysms in the brain are very dangerous, screening for new aneurysms in patients who are already struck once by SAH seems warranted. In an impressive series of articles in top neurology journals, Marieke Wermer demonstrated that 18% of these patients indeed had new aneurysms. She found that these patients had a high risk of having a second SAH. Presently a decision model is being developed to determine if screening could be cost-effective for patients after SAH in general or certain subgroups of patients with additional risk factors for a second SAH.**

SAH from a ruptured aneurysm often occurs in relatively young patients (< 55 yrs), has a very high mortality rate, and has a major impact on the life of survivors. Therefore a study was designed to evaluate the effectiveness and costs of screening for aneurysms by CT-angiography in patients who survived a first SAH. Wermer screened for new aneurysms in 610 patients by CTA, who had an initial SAH in 1985-2001 and in whom the SAH was treated by surgically clipping of the ruptured vessel. Newly discovered aneurysms were further investigated using intra-arterial angiography. Based on clinical considerations a number of the newly discovered aneurysms were treated preventively. Wermer: "Intracranial aneurysms have long been considered a once in a lifetime event. However, our studies show that many patients with a previous SAH

showed the formation of new aneurysms (about 18%) and growth of existing aneurysms. Therefore the occurrence and growth of aneurysms should be considered a continuous process" (*Brain* 128:2421-9).

In a retrospective study, Wermer revised the cases of 752 patients with a successfully occluded aneurysm after SAH to determine the risk of a second SAH. She found that survivors of SAH have a 22 times higher risk than the general population to be struck again by a stroke through SAH. Additional risk factors for recurrence of SAH were smoking, age and multiple aneurysms at the original SAH (*Stroke* 36:2394-9). Wermer also determined the yield of prospective short-term (1 year) follow-up for the growth of small aneurysms detected at screening in patients with previous SAH or with familial intracranial aneurysms. She found that the yield was very small, and did not eliminate the risk of rupture. If follow-up with an interval longer than a year is useful remains to be investigated. (*Stroke*, e-pub, 29 December).

Wermer concludes, "We have shown that patients after a SAH have a high probability to develop new aneurysms and to be struck by a second SAH. In our initial decision model (*Neurology* 62:369-75), based on literature data, we concluded that screening was not beneficial. Now we have more insight in the high incidence of new aneurysms in this patient group. We will use the results of our screening study as input for a new decision model. With this model, we will be able to determine if screening is cost-effective for patients after SAH in general or for particular subgroups of patients with additional risk factors for a second SAH such as smokers and patients with multiple aneurysms."

Marieke Wermer (MD, Utrecht University, 2000) is a resident in Neurology at the UMC Utrecht. From 2002-2005 she worked on a ZonMW grant of the Health care efficiency research programme, entitled, 'CT angiography follow-up after subarachnoid haemorrhage.' (principal investigator, Gabriël Rinkel). The work was performed and published on behalf of the ASTRA study group (UMC Utrecht and AMC Amsterdam). The studies of Marieke Wermer were performed in close collaboration with Irene Van der Schaaf (Dept Radiology, UMC Utrecht), who successfully defended her PhD thesis December last year (cum laude). Later this year, Marieke Wermer will defend her PhD thesis based on the work as described briefly in this article. She will qualify as a neurologist in 2009.



### Diabetes and schizophrenia

February 16, 2006

Dan Cohen

#### Diabetes mellitus in schizophrenia or schizoaffective disorder: a iatrogenic or endogenous problem?

D.E. Grobbee, R.P. Stolk, C.C. Gispen-De Wied supervisors

**The putative link between schizophrenia and diabetes mellitus has puzzled clinicians and researchers for many years. Dan Cohen studied the occurrence of diabetes and schizophrenia and their therapeutic treatment to find out whether co-morbidity is endogenous or whether diabetes is caused by antipsychotic drugs. Cohen's work implies that antipsychotic medication increases the risk of diabetes. He indicates that a more intensified screening for metabolic effects of antipsychotic drugs is warranted.**

Does treatment for schizophrenia cause diabetes or do people with schizophrenia have underlying diabetes or an increased susceptibility to develop it? A study of the literature by Cohen indicates that olanzapine and clozapine enhance the risk of developing diabetes more than other antipsychotic drugs. This effect is particularly well documented in patients with schizophrenia. Cohen performed an investigation of the effect of antipsychotic drugs in 481,925 subjects of the general population. He found that subjects treated with typical or atypical antipsychotic drugs have an increased risk of diabetes. These results suggest that antipsychotic drugs are associated with an increased risk of diabetes, independent of the underlying psychiatric disorder.

Cohen studied retrospectively the effect of antipsychotic treatment in 2,585 newly diagnosed diabetes patients. He found an increased risk for initiation of insulin therapy at 2 years after diagnosis of diabetes in users of antipsychotics compared with non-users. He concluded that use of antipsychotics by patients with type 2 diabetes is associated with initiation of insulin therapy, especially in the first 2 years of the disease. Conversely, in a cross-sectional

study the occurrence of diabetes in 200 schizophrenia patients with a mean age of 41 years who were under antipsychotic medication, the prevalence of diabetes was 14.5%, of which 8% was previously known and 6.5% newly diagnosed. Compared to a 1.5% prevalence of diabetes in the age-matched general Dutch population, the prevalence of identified cases was significantly increased in the study population.

Further, Cohen addressed the question whether the duration of antipsychotic treatment was related to the development of diabetes. In an exploratory cross-sectional study, the non-fasting plasma glucose level in 266 inpatients, mean age 47.5 years, with DSM-IV diagnosis of schizophrenia or schizoaffective disorder was measured. The overall prevalence of type 2 diabetes was 9%, which is significantly higher than the prevalence of 4.9% in the general population. The increased prevalence was found to be related to overweight and obesity. Nor the time of exposure to antipsychotic treatment nor duration of illness were significantly correlated with the prevalence of diabetes. Typical and atypical antipsychotics contributed equally to the prevalence of diabetes. Cohen concludes that no significant relation between long-term antipsychotic treatment and prevalence of diabetes could be found.

Cohen concludes, "Antipsychotic drugs have been found to be diabetogenic both in the general population and in patients with schizophrenia. The antipsychotic drugs seem to exert their diabetogenic effect in two different ways, depending on the duration of treatment: in short-term treatment an acute effect is found, resulting in an atypical, more severe form of type 2 diabetes. In long-term treatment the effect of the diabetogenic factors risk factors age and weight were attenuated by typical but not by atypical antipsychotic drugs. Three modifications of the monitoring protocol of metabolic effects of antipsychotic drugs are indicated: *intensification* of the screening during the first 12 weeks of treatment, and extension of the monitoring to *all adult patients irrespective of the type of antipsychotic drug prescribed*."

**Dan Cohen** (April 11, 1954, Arnhem). Secondary education (Stedelijk Gymnasium Arnhem, 1972); Medicine (Amsterdam University), MD, 1980; Philosophy (Amsterdam University), 1986. Residency in psychiatry, 1982-1983 (Gent, Belgium), and 1984-1989 (Leiden). In 1989-2005 he worked as psychiatrist in various functions in Amsterdam and Santpoort. Presently he works at the mental health care institute GGZ-NHN in Heerhugowaard.



### Jack Rabbit Award for Patrick Hanlo

Patrick Hanlo (Neurosurgery) has received the Jack Rabbit Award of the Jack Rabbit Foundation. The aim of this foundation is to generate funds to improve the quality of life, health, and education of children. Last year the board



of the Jack Rabbit Foundation visited the Wilhelmina Children's Hospital to acquaint themselves with innovative developments in paediatric care. Hanlo presented the work of his paediatric neurosurgery team during this visit. The award committee recognised Hanlo's innovative achievements to help concentrate the paediatric neurosurgery in the Netherlands. Hanlo received the award for his work as paediatric neurosurgeon and researcher, but also for his readiness to help and support the ill or handicapped child in our society. Also his great enthusiasm for his work and his ability to motivate young colleagues were commemorated. There were 8 nominees for the award, which exists of an original work of art by Clemens Briels (see photograph).

### VENI grant for Damiaan Denys

A prestigious VENI grant of the Netherlands Organisation for Scientific Research was awarded to Damiaan Denys (Department of Psychiatry) for his research proposal, *'Deep brain stimulation in obsessive compulsive disorder (OCD): exploring the mechanism of action with functional neuroimaging and in vivo microdialysis studies'*. Deep Brain Stimulation (DBS) is a non-destructive and reversible technique for modulating neuronal function that does not require the creation of a permanent lesion in the brain.

Denys will implant electrodes in the brain of patients with treatment-refractory, malignant, and intractable OCD. In a double blind, randomised, cross-over designed study he will determine the effect of electrical stimulation of the nucleus accumbens on the patients' symptoms. This will be correlated with changes in the regional cerebral blood flow. Denys will also perform mechanistic studies in which he will determine the effects of DBS on the dopaminergic system in the human brain. These patient studies will be complemented by studies on the effect of DBS on dopaminergic functions in healthy rats and in a rat model for OCD.

### Carl Zeiss Award for Saskia Van der Hel

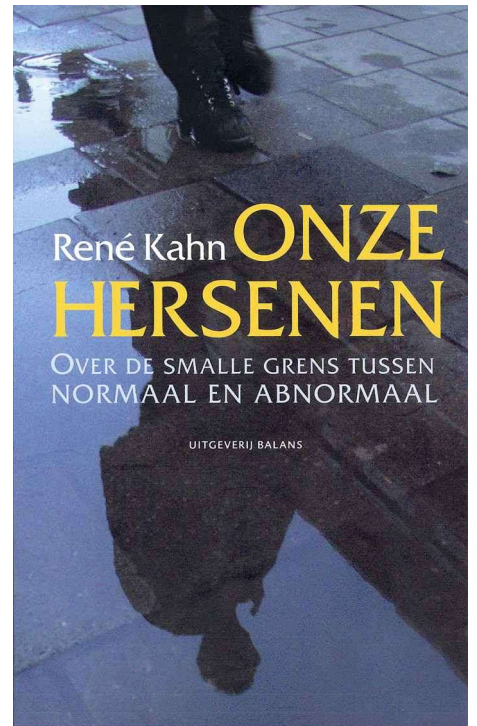
Saskia Van der Hel (Department of Pharmacology and Anatomy) received on January 7, 2006, the Carl Zeiss Poster Award of the Netherlands Society of Anatomists (Nederlandse Anatomen Vereniging). The award was presented to Van der Hel for her poster entitled, *'Genes involved in human epilepsy'*, authored by Saskia Van der Hel, Koen Van Gassen, Marina De Wit, Frank Holstege, Peter Van Rijen, Cees Van Veelen, Dick Lindhout, and Pierre De Graan.

### René Kahn about 'Our brain'

What is wrong with 'abnormal' people such as junkies, homeless, alcoholics, or obsessively cleaning housewives? Are they formed by their childhood and situation? Have they made the wrong decisions along life's road? And is it, as popular opinion has it, their own fault that they have ended up at the wrong side of the line? Scientists now develop a view which places such abnormal behaviour in the context of the genetics of these patients.

Last month the long-awaited book by René Kahn (Department of Psychiatry) appeared, *'Our Brain'*. It is written in Dutch and is a popular scientific book, meant for a broad audience. By the book Kahn brings a very important message to the general public, and that is that people are not formed per se by their personal situation. Using case studies and reference to recent scientific findings on various psychiatric disorders, Kahn explains that 'abnormal' behaviour often results from changes in the brain. Implicit in the book is the notion that changes in the brain may be caused or influenced by our genetic make-up, and thus that some people are more susceptible to develop psychiatric disorders than others. Therefore, Kahn argues that considerations regarding brain structure and human genetics have their place in modern psychiatry.

René Kahn, *'Onze hersenen'* (in Dutch), published by Balans, January 2006, ISBN 90 5018 712 9.



## **Ponsen & Looijen: Personal advice on thesis production and discounts on thesis printing**

Ponsen & Looijen Printers in Wageningen is a firm with a long tradition in the high quality reproduction of PhD theses. Moreover, Ponsen & Looijen is recommended by the Netherlands Organisation for Scientific Research (NWO). The Rudolf Magnus Institute has drawn up a contract with Ponsen & Looijen, to be able to help PhD students in the complex process of book production. This can save time and money during this, often hectic, last phase of the graduation. This offer is only valid for PhD students of our Institute, but notice that there is no obligation to make use of the services of Ponsen & Looijen.

As a result of this contract with the Rudolf Magnus Institute, Ponsen & Looijen will:

- give personal advice (on site and on demand) to all PhD students about the production of their thesis.
- once a year (October) organise a plenary meeting, in which Ponsen & Looijen will give an outline of the production process.
- offer a 12.5% discount on the printing of the thesis to each PhD students of our Institute.
- offer a special prize for the design of the interior and cover of the book of € 950 (excl. tax).
- deliver the exact amount of books as ordered without extra costs.
- provide PhD students with a book *'How to make a PhD thesis'*, with very clear instructions and information of all aspects of the book production.

All written information as well as the personal advice is available in Dutch and English. For any questions contact Joke Ploos van Amstel, Ponsen & Looijen, utrecht@p-l.nl, tel. 06-5310 5267.



## **March 3, Helmholtz Lecture**

**David F. Clayton** (University of Illinois, USA)

'Neurogenomics of bird song memory'

Venue, 'Rode zaal', Ruppert Building, Leuvenlaan 19, Utrecht, 16:00-17:00. Contact, v.maassen@fss.uu.nl

## **March 9, Meeting of the Netherlands Society of Psychophysiology**

Venue, University Library, Heidelberglaan 3, Utrecht, 10:00-16:30. Contact, k.b.e.bocker@pharm.uu.nl

## **April 19-27, Course on Neuropsychopharmacology**

The course on Neuropsychopharmacology is accredited by the Rudolf Magnus Graduate School of Neuroscience and will be awarded by 7 credits. Venue, partly in Amsterdam, Weesp, and Utrecht. Programme, <http://www.rudolfmagnus.nl>. Registration, [eam.borghols@vumc.nl](mailto:eam.borghols@vumc.nl)

## **May 4-5, Meeting of the Association of European Psychiatrists - Neuroimaging Section**

'Neuroimaging Change over Time in Psychiatry'

Venue, Academy Building, Domplein 29, Utrecht.

Programme and registration, <http://www.rudolfmagnus.nl>

## **August 28-29, Rudolf Magnus-Helmholtz Summerschool**

Mark your agenda for the joint Summerschool of the Rudolf Magnus and Helmholtz Graduate Schools.

Venue, Conference Centre Ottone, Kromme Nieuwegracht 62, Utrecht. Programme to be announced, check our website for updates, <http://www.rudolfmagnus.nl>

## **September 8-9, Brain Days**

A two-days meeting with international experts on the theme, **'Brain plasticity in children'**.

Venue, UMC Utrecht. Programme to be announced, check our website for updates, <http://www.rudolfmagnus.nl>

## **November 8, Rudolf Magnus Symposium**

Including the Rudolf Magnus Lecture 2006 by

**Frans De Waal** (Emory Univ. Atlanta, USA)

and the announcement of the winner of the Rudolf Magnus Research Award 2006.

Venue, UMC Utrecht, 13:30-17:15. Programme to be announced, check our website for updates, <http://www.rudolfmagnus.nl>. Contact, m.vandenadort@med.uu.nl

## **November 8, Rudolf Magnus Evening**

A unique mixture of social and scientific events is organised following the Rudolf Magnus Symposium.

Venue, UMC Utrecht, 18:00-21:00, programme will include diner, details to be announced. The evening programme is freely accessible for all members of the Rudolf Magnus Institute. Registration is required, contact, m.vandenadort@med.uu.nl

## **November 16-22, Introductory Course for PhD students in Neuroscience**

Information and registration, <http://www.rudolfmagnus.nl>

## **November 23-24, Annual Meeting PhD students**

Venue, Conference Centre Woudschoten, Zeist.

Information and registration, <http://www.rudolfmagnus.nl>