Public accountability lecture
Prof. Dr. Merel Ritskes-Hoitinga
23 april 2016

World Day for Animals in Laboratories

Ladies and gentlemen,

I am very pleased that all of you have come here today to reflect with me on the use of laboratory animals. Tomorrow, 24th of April, will be World Day for Animals in Laboratories.

I am giving this Public Accountability lecture because I believe we would do well, both for ourselves and for everyone around us, to be very aware of what we do with laboratory animals, what benefits we derive from them, and at what material and immaterial price. It is a valuable exercise for all of us to contemplate our work with some regularity, to evaluate it thoroughly, and to reflect on it with our hearts and minds. But this is especially true for work involving laboratory animals.

When I was staying in Japan in 1986-1987 and made my first steps in the world of animal research, I was introduced to an impressive annual ceremony, in which all the university's doctors and researchers held a meeting to thank and commemorate the laboratory animals. A wonderful tradition that is much in keeping with Asian culture. In the same spirit, I would also like to dedicate my lecture to all living creatures whose lives were sacrificed for the well-being of others, hoping to contribute to reducing the unnecessary suffering of humans and animals alike. Beyond commemoration, however, I would particularly like us all to reflect on our use of laboratory animals as a cultural addiction instead of considering rationally, as is our habit, whether animal experiments are still required, and if so, which ones.

Shimane Medical University, Izumo, 1987

The Dean lays flowers at the altar.

Animal experiments: ten years past and ten years forward

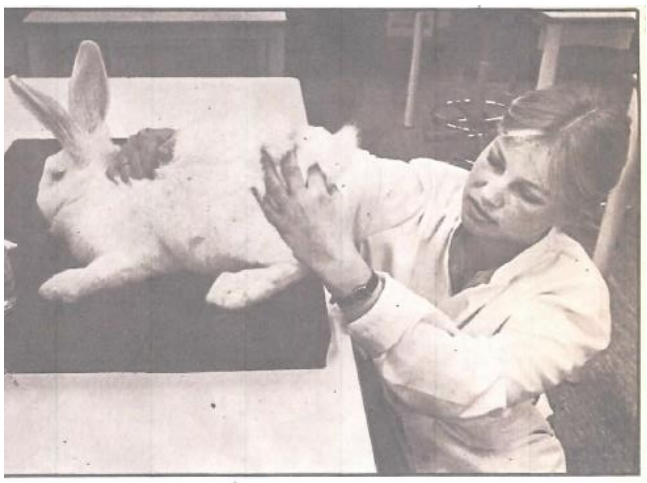
A little more than ten years ago, I was appointed Professor of Laboratory Animal Science and head of the Central Animal Laboratory (CDL). Let me first take you back to what has

happened in those ten years, before taking a look at our goals for the next ten years.

I have been working in this field for thirty years full-time. It was in 1986, when I was still a student, that this domain of science first enthralled me. I was writing a literature study on atherosclerosis in the rat (subsequently published as Ritskes-Hoitinga & Beynen 1988). Professor Bert van Zutphen and Professor Anton Beynen were my inspiring supervisors. I collected all the literature I could find on the use of the rat as a model for studies of cardiovascular diseases in humans, summarizing everything in big handwritten tables. It was donkey work, but this was the moment when my mission became clear to me.

I concluded that animal experiments left a lot to be improved and that this was what I wanted to dedicate myself to. Many studies were clearly sloppy, meaning you could not tell what had been done with the animals in practice, which made it impossible to assess their relevance. Cardiovascular diseases were induced by many different dubious methods, and only few researchers had the patience for cardiovascular diseases to arise spontaneously in the rat in old age. This proved to be the case but was neither registered nor followed by others. Many did not have the patience to wait for the animals to age and hence gave them very high dosages of vitamin D in their feed to speed up the advance of cardiovascular disease. In some studies, the animals were given so much vitamin D that half of them died before the end of the trial. It was entirely unclear why they had chosen this trial design, and the only explanation, therefore, must be that they were in a hurry to get their next paper published. The process of cardiovascular diseases as induced by vitamin D differed from the same process in humans substantially, and therefore questions the human relevance of these studies.

This made it clear to me how much room for improvement there was, both in terms of scientific quality and in terms of animal welfare. And the latter in particular warmed my veterinarian's heart. A question people often ask me is: if you're a vet, should you really be doing this? From my perspective, the answer is: yes, it is precisely us, who care about animals, who are in a position to make a difference, by pursuing first-rate science and animal welfare at the same time. It was and is my mission, therefore, to prevent unnecessary suffering and to promote the welfare of all living beings.



Utrecht University Magazine 1988

Why a Public Accountability lecture?

Jan Jonker, Professor of Sustainable Entrepreneurship at Radboud University, was the first professor in the Netherlands to give a Public Accountability lecture after his first five years in office and to put forth his vision for the years to come. A Public Accountability lecture is something of a novelty in science, but the many positive reactions I received when I announced my intention to give one lead me to believe that many more may follow suit. The goal of this Public Accountability lecture is to be publicly accountable for my activities up to this point and for my mission for the future. I feel that society and the tax payer are entitled to it, but I also enjoy doing it and hope to be able to rally your support for the future. I will certainly be needing society's support, for my mission is not a minor one.

Scientific quality, animal welfare, and patient well-being are all at stake in my field of science, and any innovations in these domains are rarely received to great critical acclaim. Animal experiments are ethically contested and are, by definition, a source of debate in society. As one of my tasks is to speak to the press, I am often facing society's extreme points of view on the issue. It is important for science to be accountable for what it is doing, how it is doing it, and what results it is producing for patient care. It is something of a catch-22 situation though: society is doing a lot of criticizing, but that very same society is investing billions in medical research and animal studies to exclude risks to human beings. So, from society's perspective, how are we doing?

What is the purpose of animal experiments?

In a university medical centre such as Radboudumc, animal experiments are largely performed to promote human health and well-being. The toxicity of potential new drugs, for instance, is first tested on laboratory animals. The effectiveness and possible side-effects of new medicines, moreover, are also first tested in animal experiments. Generally speaking, we can distinguish between animal experiments that 1) have a direct link with the clinic, so-called translational research, and those that 2) generate new knowledge whose relevance for the clinic is not yet immediately apparent.

In this latter category, you might think of research into how the brain works, aiming to improve our long-term understanding of conditions such as dementia and Parkinson's disease so as to be able to provide better treatment methods or even preventive measures in the future. With a view to our ageing population, it is essential that we pay more attention to the prevention of chronic diseases. This latter category of research is called fundamental research, which is important in advancing our knowledge. In 2015, 72% of the animal experiments at our university were translational, and 18% were fundamental.

The history of the Central Animal Laboratory

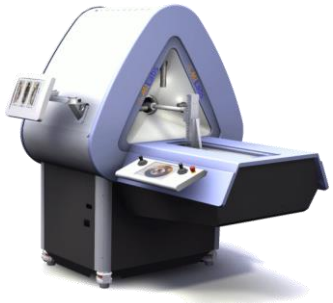
In 2015, the Central Animal Laboratory (CDL) celebrated its 60th anniversary. When it opened its doors in 1955, it was probably the first laboratory in Europe, if not the world, that became a centralized facility thanks to the forward-looking sense of its first director, Rien Dobbelaar. Rather than having a multitude of laboratories all over campus, the animals were

now housed, looked after, and treated in a single location. This not only made the work a lot more effective, as the lab took on animal caretakers specialized in looking after and treating animals, but it also truly improved the quality of work and animal welfare. The lab's management also began to specialize in laboratory animal science, all serving to enhance scientific quality as well as animal welfare.

Staff in an animal laboratory love animals and want to make a difference. If animals are to be used to help improve human health, they should be suffering as little discomfort as possible. Their welfare should also be improved, moreover, by housing animals like rats and mice in ways that benefit their social life and by offering them cage enrichment devices such as treadmills and nesting materials. On a global level, cage enrichment has by no means become standard procedure, and it has only been common in the Netherlands for a few decades.

The successor of Rien Dobbelaar as CDL director was Wim van der Gulden, who was also appointed to the special chair of Laboratory Animal Science by the Dutch Foundation for Laboratory Animal Information. In 2015, I succeeded Joop Koopman as director of the CDL. From 1997-2005, I had been head of the Biomedical Laboratory and Professor of Laboratory Animal Science and Comparative Medicine at the University of Southern Denmark in Odense. I remained Professor of Laboratory Animal Science here in Nijmegen thanks to research director Professor Carel van Os and the then Dean Professor Dirk Ruiter, who felt that combining the directorship with the professorship was important as this would help to profile research and education in laboratory animal science in the CDL's everyday practice.

From the moment of its establishment, the CDL has engaged in an open dialogue with society, a tradition that I have not only continued but that I am also proud of. It is vital for us to have such an open dialogue because society may expect us to be accountable for what we do. An open dialogue will also keep science on its toes and prevent it from becoming too complacent. This long tradition of openness of the CDL and this university has many advantages now that calls for transparency are growing. For many years now, for instance, the CDL has adhered to the Openness Code that was adopted and signed by three nationwide scientific organizations in the Netherlands: the KNAW, the VSNU, and the NFU. This code was adopted to impel their member organizations to produce open annual reports on animal experiments. The CDL has observed this code in its annual report, which is accessible to anyone on the CDL website.



Openness

Openness also means that we do many conducted tours of the facility, that we regularly talk to the press, and that we allow footage to be shot at the CDL if this does not upset studies. Organizations opposed to animal testing are also welcome to take a look around. We have given tours, for example, to Proefdiervrij, to the Belgian organization Biteback, and to the Anti Animal Experiments Coalition, now Animal Rights. We invite teachers from the Proefdiervrij organization to take part in our laboratory animal science courses to make sure that our future researchers are informed about their points of view. The Animal Rights organization visits us every year for an open dialogue with the licensee and the undersigned, and we exchange points of view in these meetings. You will understand that we do not reach agreement on all issues, but we do manage to foster an understanding for one another's standpoints and arguments.

14 February 2011 (Valentine's Day), De Gelderlander Newspaper
Presentation of a petition against research on primates

Politics in the Netherlands

The Netherlands is unique in the world in having animal interests specifically represented in its Lower House: the Party for the Animals. The CDL has established excellent contacts with Esther Ouwehand, who is a Member of Parliament for the Party for the Animals and who has also visited the CDL several times to be informed about the scientific process. In 2011, the Parliamentary Standing Committee for Public Health, Welfare, and Sport, which was the Lower House committee responsible for animal experiments at the time, also paid a working visit to the CDL. Most Members of Parliament had never visited an animal laboratory before and greatly appreciated our invitation. This exchange was most useful to us too, as it helped us grasp the workings of politics in The Hague.

Partly in consequence of the visit of these Members of Parliament, a motion was adopted in the Lower House in 2012 requesting the Government to consider systematic reviews of animal experiments as the standard, just as this was already the case for clinical studies. All parties voted in favour of this motion, except for the Liberal Party, which, I believe, was not unrelated to their being absent from the working visit and, therefore, lacking essential background information. A second motion, partly prepared by us, helped to make information on systematic reviews of animal experiments a compulsory part of

laboratory animal science courses. I will come back to systematic reviews at a later point in my lecture.


Parliamentary Standing Committee pays a working visit to the CDL, 2011

Lower House Motion 8 February 2012 The Lower House, having heard the deliberation and concluding that "systematic reviews" are standard procedure in medical science but not in laboratory animal research, requests the Government to make sure that "systematic reviews" will become the standard in research with laboratory animals as they are in regular science, and proceeds with the order of the day.

- Tabled by: Ouwehand (PvdD), Van Dekken (PvdA), Voortman (GL)
- Status: Adopted
- For: PvdD, SP, PvdA, GL, D66, SGP, CU, CDA, PVV
- Against: VVD

Animal experiments in the past ten years

The field of Laboratory Animal Science is dominated by the 3Rs, denoting Replacement (replacing an animal experiment by computer simulation, for instance), Reduction (obtaining the same results with fewer animals by improved use of statistics), and Refinement (lowering discomfort and improving welfare). With funding by the then licensee, I established the 3R Research Center in Nijmegen in December 2006. The aim of this Center was to support researchers in finding and applying 3R opportunities. About thirty search requests were received each year in 2007-2008, and the service was positively reviewed by researchers. In 2009, when the funding was used up and the 3R Research Center was forced to charge money for its search services, not a single search request was filed ever again 'because it costs money!'

This finding led us to investigate by way of a survey how the research world regarded the 3Rs, which became the first part of Judith van Luijk's PhD thesis. What the survey showed was that researchers did think the 3Rs were indeed important but that they were definitely not a top priority. This is also apparent from the fact that funding agencies generally refuse to make funds available to this purpose, even though, contradictory enough, they do expect the 3Rs to be applied. It is unclear, then, who should regulate and

finance it. And so, researchers spent very little time on searching for the 3Rs, about one to three hours for each application to the committee responsible for the ethical assessment of animal experiments, while a good-quality search will take several days on average. Researchers indicated that they might be overlooking existing 3R opportunities and, hence, might be failing to apply them in practice. Strictly speaking, this meant they were operating unlawfully, as the law has made it mandatory to apply existing 3R opportunities.

Considering these outcomes, we decided to take stock of where exactly the available 3R information was to be found. It turned out there were over a hundred 3R databases and websites, each with its own structure and content, which made any effective search virtually a mission impossible. So, strictly speaking, it may well be unlawful not to apply the existing 3R opportunities, but what are you to do if they are all but untraceable? Any inter-database coordination proved to be lacking. Building your own 3R database was considered a nice way to profile yourself, your own research group, your own institute, or your own country.

As is so often the way of the world and of science, an international coordinating body was also lacking. Joris Luijendijk has said that the financial crisis arose because no one was in charge: the cockpit was empty. In our field, unfortunately, we must also conclude that the cockpit seems empty, but let me promise you that, in the years to come, I will do my utmost to have this cockpit staffed with some highly expert and motivated people. This cockpit is called SYRCLE, and I will be telling you more about it later.

Changeover from the 3Rs to systematic reviews

These disappointing experiences, knowledge development efforts, and 3R survey outcomes meant that, in 2009, we concluded that the road of the 3Rs was not effectively leading anywhere. And so we decided to change over to systematic reviews (SRs), as this is a methodology that will prove to be more results-driven. After hearing a lecture by clinical neurologist Malcolm Macleod, in the period when I was beginning to have grave doubts about the effectiveness of the 3Rs, I thought: 'This is it!'

Macleod had started to do systematic reviews of animal experiments routinely because he wanted to improve his treatment of patients with cerebral haemorrhage. It had struck him that numerous positive results of animal experiments were being reported in the professional literature, but that only very few of these therapies could be applied in the clinic with any kind of success. So what was going on? By systematically mapping all available

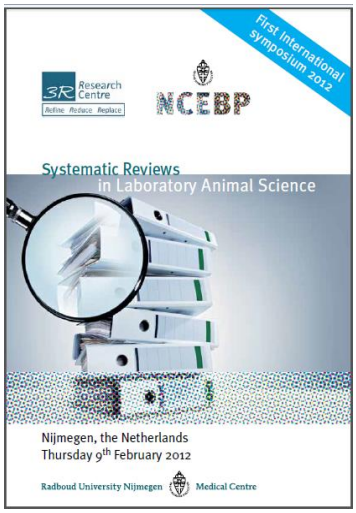
information in systematic reviews, this process could be made transparent, thus making clear what actually happened in the translation process from animal experiment to patient treatment.

Because of its usefulness and effectiveness, the systematic review methodology has been routinely applied in clinical studies on humans since 1992 and is being coordinated by the globally operating and, in our world, highly respected network of the Cochrane Collaboration. As animal experiments are done to assess the safety and efficacy of new therapies for humans, it is remarkable that it should have taken so long for this methodology to be used in animal experiments too. The first systematic review of animal experiments, incidentally, was published by a Dutch physician, Janneke Horn, in 2001.

Malcolm Macleod established the global CAMARADES network, specializing in systematic reviews of animal experiments in the field of neurology. In 2012, together with my group, I founded SYRCLE, which focuses on systematic reviews of animal experiments in general and on systematic review education in particular.

SYRCLE's foundation

From 2008 onwards, our 3R Center began to focus on the development of systematic reviews of animal experiments, and in 2012 we hosted the first international symposium on systematic reviews of animal experiments here in Nijmegen. It was at this symposium, on 9 February 2012, that SYRCLE was officially launched. SYRCLE stands for SYstematic Review Center for Laboratory animal Experimentation. And on 10 February of that same year, we also organized the first international workshop in the field of systematic reviews of animal experiments.



First international symposium on systematic reviews of animal experiments on 9 February 2012 and workshop on 10 February 2012

SYRCLE's educational activities

Thanks to funding by ZonMW, amongst others, SYRCLE was able to start offering free courses in the Netherlands, and we gave six workshops in the first two years. Participants in these workshops who wanted to do systematic reviews in actual practice were also offered coaching and supervision by SYRCLE staff afterwards. Out of the 120 participants in these six workshops, about thirty undertook to perform their own systematic review in actual fact. The first systematic review in Nijmegen was done by gynaecologist Joris van Drongelen (Van Drongelen 2014). Clinicians are used to systematic reviews, are aware of their immediate benefit for patients, and are quick, therefore, to adopt the methodology.

With funding by the Ministry of Economic Affairs, responsible for the Animal Experimentations Act, SYRCLE was able to develop guidelines to facilitate the performance of these reviews. We also received funding to produce an international e-learning module, which was completed in October 2015 and launched at the symposium celebrating the CDL's 60th anniversary. This e-learning module is also offered free at the international level. A Radboud University foundation, called the Reinier Post Foundation, also granted us funding to be able to boost on-campus teaching and coaching.

SYRCLE's international activities

Because the Cochrane Collaboration dedicates itself to systematic reviews of clinical studies to promote healthcare, we contacted them. As animal experiments are also performed for the benefit of healthcare and our goal is, therefore, the same, we felt it would be mutually beneficial to join forces. The Cochrane Collaboration replied at first that it only intended to deal with clinical studies, but when we persisted, SYRCLE was invited to be the very first to be giving a workshop and holding a meeting on systematic reviews of animal experiments at a Cochrane Collaboration conference. This took place in Quebec, Canada, in 2013.

Meanwhile, the Cochrane Collaboration has invited SYRCLE to submit an application for the establishment of an official working group on animal studies. Since our foundation, developments in systematic reviews of animal experiments at the international level have been fast and furious, and SYRCLE staff are now participating in many international networks, such as the Evidence-Based Research Network, CAMARADES, Evidence-based toxicology, GRADE for animals, and Evidence Synthesis International.

SYRCLE members attending the Cochrane Colloquium in Quebec, 2013

Participants in the special meeting on systematic reviews of animal experiments, Quebec, 2013

The Next Ten Years

The advantage of formulating a concrete global target

In 2016, Meggie Pijnappel received her doctorate degree at Radboud University's Institute for Science, Innovation and Society with a PhD thesis entitled *Lost in Technification*. After thorough study, she came to the hard-boiled conclusion that lowering the number of animal experiments by introducing alternatives is an illusion. In her words, 'Laboratory animal policy is straying and shooting off in all directions.' And so she drew the same conclusion that I did: there's no one in the cockpit.

Meggie Pijnappel has formulated the following recommendations for laboratory animal policy in the Netherlands:

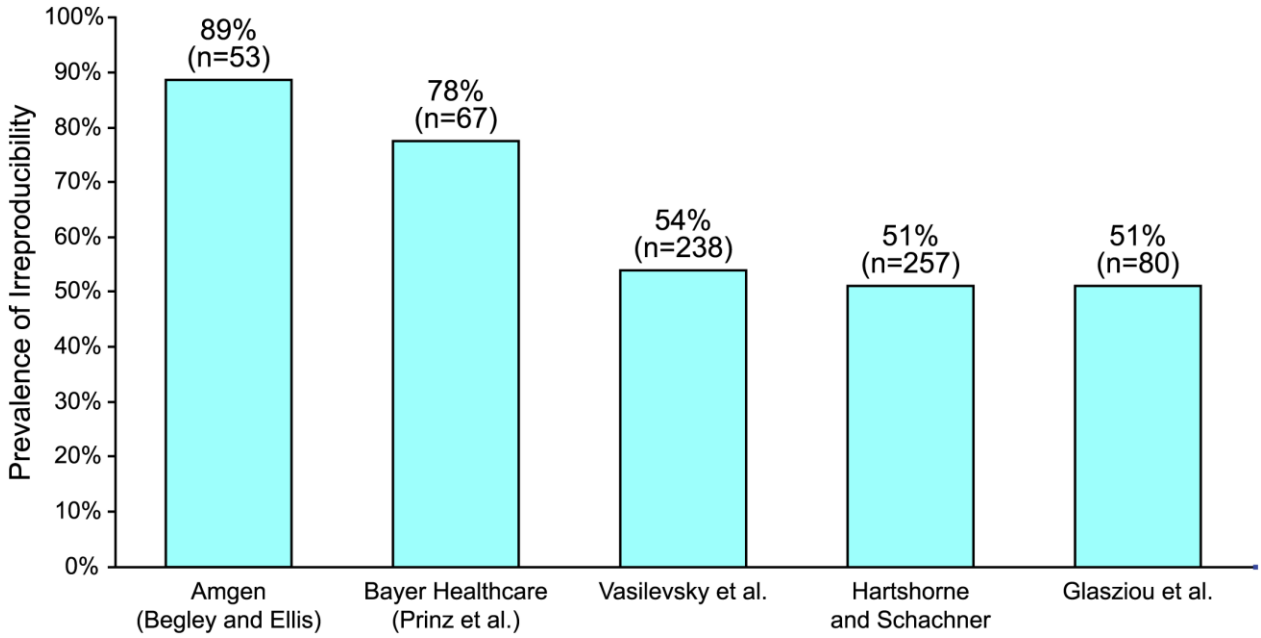
- to develop a sustainable vision;
- to make things more consistent and coherent;
- to focus on demand-driven non-animal innovations;
- to adhere to evaluation guidelines.

Great recommendations, but what is the point of policy without goals? In our field, however, goal-setting is a taboo. Whatever concrete goal you formulate, there is always someone to disagree, and so everyone is on a journey of their own and that's just how things are shooting off in all directions. Nor did Meggie venture to formulate any concrete goals in her PhD thesis, but I believe we can no longer justify working without setting goals.

In the domains of technology and economics, it is quite commonplace to formulate targets, such as a 2% economic growth target in the next year. The advantage of goals is that they create transparency, help us to make choices, allow us to assess whether we are heading in the right direction or not, and to make adjustments if necessary. Policy is a deliberate course of action in pursuit of a stated aim, and the cockpit cannot remain unmanned in such a pursuit. It requires considerable political will and courage, however, to set and accomplish goals. In 1961, it was John F. Kennedy's goal to put a man on the moon, which required a huge technical and scientific endeavour, and all of us know that this became a reality by 1969. This is how fast it can and should go.

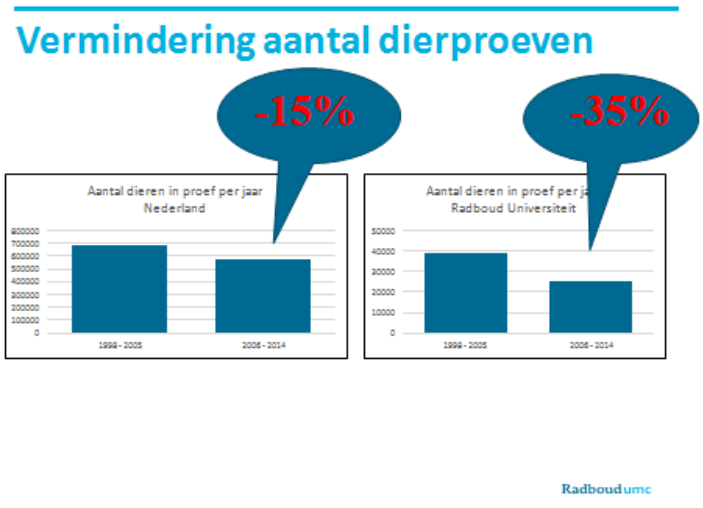
On the basis of knowledge, experience, and understanding, I have formulated the following global target: ½N-2Q-4P. A global target, because science is a global enterprise. If you were to pursue this target in the Netherlands alone, you would run the risk of getting out of sync with the rest of the world, with all its consequences. The Netherlands could, for instance, set the trend in our field together with the UK, but it is only together that we can achieve the goals we have set ourselves.

½N: can we globally halve the number of laboratory animals?



Freedman 2015

A scientific study only has any value if it is reproducible. An analysis of the literature showed that between 51 to 89 per cent of preclinical research is irreproducible (Freedman 2015, see Figure). The costs of these irreproducible tests to the US, for example, are estimated to be 12 billion dollars a year. With better-quality studies and better reproducible tests, we can lower the number of experiments by at least 50%, for if studies are performed and published to a higher quality standard, this will raise their reliability and prevent experiments from having to be redone unnecessarily.



Reducing the number of animal experiments

In Nijmegen, where we try to set the example, the number of animal experiments has gone down by 35% compared to the period before my appointment; in the Netherlands, it went down by 15% in the same period. Let's define one animal experiment as one animal that took part in one experiment. In the Netherlands, the number of animal experiments went down from 681,000

experiments a year in the 1998-2005 period to an average of 580,000 a year in the 2006-2014 period. At Radboud University, 39,000 animal experiments a year were performed between 1998 and 2005 and 25,000 a year since my appointment. This amounts to a 35% reduction while keeping scientific production constant, and so we achieved a lot more per animal. This matches the target that I set five years ago.

Because I am a professor as well as head of the CDL, research results found in my field can be translated into practice straightaway. This synergy between research and practice is an important factor in the significant reduction we achieved in the number of laboratory animals used. At one point, I called in the help of a statistician who looked at all proposed studies to calculate how many animals would be required in an experiment and how randomization and blinding requirements could be met. This at first caused virtually all proposals to be adjusted. Our excellent collaborative ties with the CDL's advisory council, consisting of researchers using the CDL facilities, are another main factor. Together with them, we drafted a joint quality guideline.

2Q: can we double the quality of studies?

In 2014, an analysis was made to investigate the compliance of 400 journals with their own quality guidelines, the so-called ARRIVE guidelines, for the publication of animal studies (Baker 2014). It was shown that, since these guidelines had been adopted in 2010, hardly any improvement had been made. Important details of animal studies are still not being published, and if such details are not published, it is impossible to reproduce a test, let alone interpret data properly.

In order to meet the ARRIVE guidelines, moreover, quality criteria like randomization and blinding should be met right from the design of the experiment. This will raise expenses for each individual study, but, in the long term, it may reduce overall expenses in a wider perspective as we will be having better-quality and, hence, more reliable results. Systematic reviews demonstrate that in about 80 per cent of cases studies fail to meet the two basic principles of scientific research: randomization (randomly allocating animals to groups and to the animal room) and blinding (not knowing what group gets what treatment). With regard to quality, therefore, there is a world to be won.

Greater relevance can also be achieved in one's choice of animal model. An analysis of the number of available animal models for cartilage defects in humans showed that such studies often use rodents (de Vries 2012). This is an opportune choice if you aim to obtain positive results and publication in high-ranking scientific journals, but as a model for the condition in humans, it is virtually pointless. When a defect is introduced into a rodent's cartilage, the condition will always reach down into the bone tissue as the layer of cartilage is so thin that the body itself will repair the defect when blood vessels grow in.

In humans, however, the defect generally remains restricted to the cartilage, which prevents the body from healing itself as there are no blood vessels in cartilage. A larger animal model such as the goat, the sheep, or the pig is much more suitable, therefore, as a model for this problem in humans. The same is true when replacing tissue removed from a bladder in the case of cancer (Sloff 2014). If we opted not to use rats or mice in this type of experiments, we would get more relevant results for humans with much fewer animals.

4P: can we quadruple patient relevance?

To optimize patient relevance, I contacted the chairwoman of the Radboudumc-wide patient advisory council, Jopie Verhoeven, to explore with her how patients can be involved in our everyday research practice. And I am happy to tell you that my contacts with the patient council, as personified by Jopie Verhoeven, really add extra lustre to my work, for patients are the be-all and end-all of our efforts. And so, Jopie, I am very happy you have joined us here today.

To my knowledge, such a developing collaboration between an animal lab and a patient council is unique in the world. We are now also collaborating more closely with patients and patient associations, such as ReumaZorg Nederland, in another NWO project. Involving patients in research is very important.

Dierproef heeft vaak weinig praktisch nut

Dierproeven leveren weinig op voor de medische praktijk, constateert **Frans Stafleu**. Er moet veel verbeteren om de resultaten vertaalbaar te maken naar patiënten.

Deze krant berichtte op 26 januari over dierproeven waarvoor apen autistisch waren gemaakt. Er was besloten de proeven te doen met apen, omdat onderzoek met ratten te weinig opbracht. De volgende dag schreef de redactie naar aanleiding hiervan dat 'alleen dierproeven waarvan nut en noodzaak onomstootelijk vaststaan' mogen worden gedaan.

Als we het over dit uitgangspunt eens zijn, hebben we een serieus probleem. Want uit onderzoek blijkt dat gegevens uit dierproeven maar heel beperkt van nut zijn voor de kliniek. De discussie gaat dus niet alleen over de 'autistische apen', maar als eerste om de algemenere vraag hoe je naar dieren meestal niet terug; ze zijn vaak jong, van één geslacht, genetisch identiek en gezond. Onderzoekers gebruiken deze 'gestandaardiseerde' dieren bewust. Ze kunnen zo met meer zekerheid vaststellen dat meetresultaten echt het gevolg zijn van de behandeling, en niet van andere verschillen tussen de proefdieren.

Meer gevarieerd

Behandelingen die ontwikkeld zijn in zo'n gestandaardiseerde groep proefdieren, werken vaak niet bij patiënten, waarschijnlijk doordat die zo'n diverse achtergrond hebben. Dit probleem oplossen is niet makkelijk. Wellicht moeten we met meer gevarieerde proefdieren werken, of meer gebruikmaken van wat we weten van de patiënten.

TF1-3, TF1-4

Een van de 'autistische' aapjes

NWO project team and opinion editorial in *Trouw* on this NWO project

I already mentioned the cartilage example to show how we demonstrated in a systematic review that a better choice of model can help to obtain better clinical results with fewer animals. In general, the patient relevance of animal experiments is very disappointing. For cerebral haemorrhage (Howells 2012) and multiple sclerosis (Vesterinen 2010), for example, analyses have been made of the number of animal experiments that were published with positive treatment results, and the number of those that actually proved to be effective in patients in the clinic. Out of about a thousand positive results, only four proved to be effective in the clinic. This is a success rate of just 0.4 per cent. There is a lot to be gained in this area.

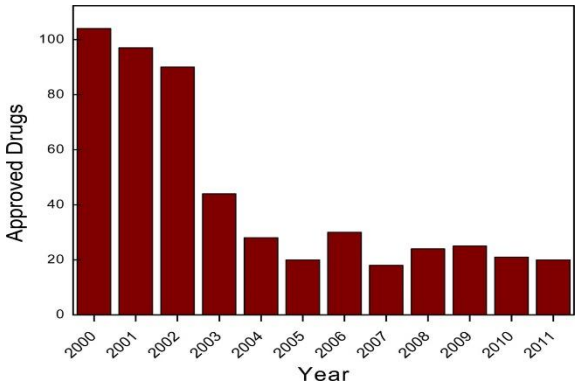
If randomization and blinding requirements are not met, studies tend to get results that are too positive for the effects of a new treatment. This may mean that a clinical trial is launched on the basis of the positive results of one or several animal studies, and that this clinical trial may then show that the new therapy is not working after all.

The Dutch physician Janneke Horn was the first in the world to conduct a systematic review of animal experiments when the drug Nimodipine proved not to be effective in a clinical trial of patients with cerebral haemorrhage, whereas animal studies had shown such apparently promising results. She then decided to undertake a systematic review of all

evidence from animal studies (Horn 2001), which demonstrated that Nimodipine had not actually had any effect in animal studies at all! It also happens repeatedly that animal studies are undertaken while clinical trials have already been started. Why? Because there is no one in the cockpit and we do not know where we are heading.

Let me give you another example of a clinical trial that found very severe and serious side-effects (intracranial haemorrhages) when applying thrombolysis (the breakdown of blood clots) as a therapy in Stroke. The individual animal studies had not shown any side-effects, but if you examined all animal studies together, you saw exactly the same side-effects that would subsequently occur in patients (Pound 2004). This could have been predicted and prevented. These examples, therefore, underline the importance of conducting systematic reviews of animal experiments to prevent people from being exposed unnecessarily to clinical trials whose non-effectiveness can be predicted.

Loscalzo (2012) made an analysis of the number of drugs that were approved by the American Food and Drug Administration for market release. The Figure below clearly shows a downward trend. One of the reasons mentioned to explain this trend is that many studies have a narrow focus on a tiny research area, such as a cell or a receptor. When a drug enters the body, however, it will affect not only this one cell or receptor but also many other processes. If this has not been taken into account in a study at an early stage, the drug will not make the grade in the approval process. It is important, therefore, for the entire organism and the operative mechanism to be involved in studies. Systematic reviews can play a major role here.



Loscalzo 2012

Clinical trial makes headlines: PROPATRIA

A clinical trial that made headlines in the Netherlands was the so-called PROPATRIA trial because too many people in the treatment group died unexpectedly. Patients with acute pancreatitis were treated with “good bacteria”, the so-called probiotics. The trial was terminated after an unexpectedly high number of people in the treatment group had died. The media made mention of people’s astonishment at this result as prior animal experiments had been performed without a hitch.

In this type of medical issues, the media often come up with a general statement like this. The appropriate questions to ask in this case, however, are: how have these animal experiment been performed? Have they been performed properly? Have the right models been used? And is the treatment process at all comparable with that of humans? SYRCLE decided to conduct a systematic review of the animal studies that had preceded the clinical

PROPATRIA trial (Hooijmans 2012). What did we find?

1. The composition of the probiotics used in the animal experiments differed from that used in humans;
2. The therapy was administered at different points in the disease course;
3. The probiotics were administered at different locations.

These differences alone render these animal studies incomparable to what was done with these patients in the clinic. This example then raises the question how a medical ethical committee analyses and weighs the evidence of prior animal experiments when approving a medical experiment like this one.

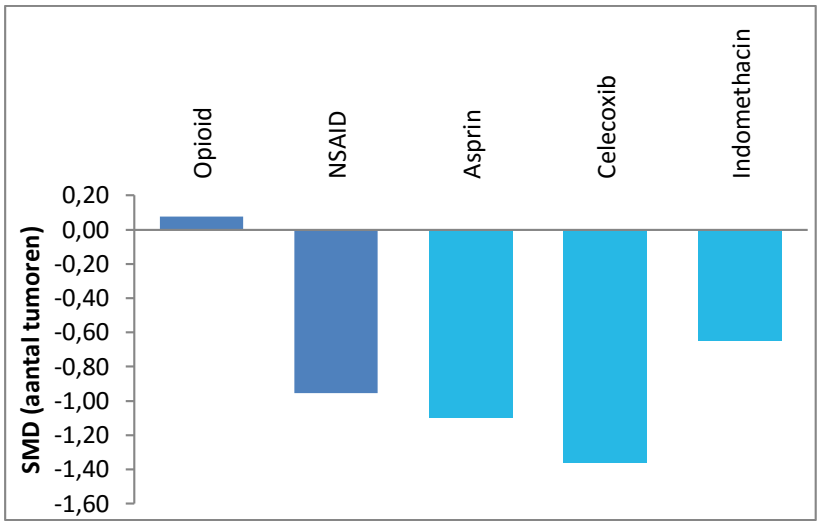
Systematic review makes promising discovery: aspirin inhibits cancer in laboratory animals

Fortunately, systematic reviews serve not only to find out what went wrong where in retrospect but also to gain new insights that may be highly clinically relevant. Although no more than about 25 full-scale systematic reviews have so far been performed in Nijmegen, we have already made a remarkable discovery.

Clinicians, concerned if the use of painkillers might possibly promote tumour growth and tumour metastases, turned to SYRCLE with the question if it would be possible to perform a systematic review of the outcomes of animal studies in this field. After thorough analysis of all available studies, we were able to reassure them. The use of morphine-type substances, called opioids, proved to have no effect on tumour metastases in laboratory animals; aspirin-type substances, also called NSAIDs, even had a lowering effect on the number of metastases of several types of cancer. All aspirin-type substances, including aspirin, celecoxib, and indomethacin showed a significant reduction in the number of metastases after application.

Because this effect was found for various types of cancer and in different circumstances, it is expected to be the same in humans. This is a promising result for further study in humans, as aspirin is a simple and inexpensive medicine. If I extrapolate the results of some animal experiments with a high metastasis-reducing success rate to human dosages, we would be requiring 500 mg of aspirin two to three times a day. Animal experiments already show significantly fewer metastases in relatively short treatment periods (14 to 48 days), but as metabolism in rodents is much faster, I expect that treatment periods in humans should be longer to be able to measure the same effects.

So without having done a single additional experiment, we found proof that NSAIDs reduce the number of tumour metastases in laboratory animals. Our findings were published in the scientific journal PAIN (Hooijmans 2015), and we are now considering a follow-up publication to examine this effect in greater depth. Aspirin and aspirin-type substances may prove to be offering a much cheaper and much more effective treatment of cancer than we had assumed so far. Together with the clinic, I hope to be able to undertake several studies on the effects of aspirin on cancer before the year is out.



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Ladies and gentlemen, let me summarize my lecture. Science is a global business. So parallel to developments on the World Wide Web, let us undertake to accomplish a similar collaborative effort in our research domain. It is feasible. But we need a target. In my lecture, I have argued that it is possible, with half the number of laboratory animals, to double the quality of studies and quadruple their relevance to patients.

On a global scale, this would mean a reduction of more than 50 million laboratory animals a year, as the number of animal experiments performed globally is estimated to be 115 million. For people working with laboratory animals, it is of the utmost importance that their work with laboratory animals is scrupulously performed to prevent an unnecessary burden on humans and animals alike.

In addition, the effect on science and on patients' health and welfare will be significant. If the inhibiting effect of aspirin should prove to be translatable to humans in actual fact, this means that one systematic review in a total of 40 systematic reviews is actually translatable. This would amount to 2.5 per cent translatability, which is six times as much as the 0.4 per cent we are currently achieving.

A Word of Thanks

In his 2016 New Year's speech, the chairman of the Board, Gerard Meijer, suggested we should spend some thought on whom you would like to thank this year. I found this very inspirational, just like Paul van Tongeren's beautiful farewell speech on the same theme of gratitude. We would be nowhere without other people, and we would do well to be aware of this truth with some regularity. It will make you realize how many people have played a significant role in your growth and how many people have lent you their support. Not to be taking this for granted helps to deepen my feelings of gratitude and makes me very happy indeed.

When I look back on those who have played a crucial role in my work and my development, there are so many. I will name them here, at the risk of overlooking people, to whom I like to apologize in advance. My parents, heit (in memoriam) and mem, taught me that it is important to learn as much as you can, for that will always serve you well in the future. I am learning every day and enjoying it every day. My secondary-school biology teacher, van der Hurk, laid the foundation for me to enjoy doing research. He gave me a 10 for a poster presentation on doing biological field research. My sister Minke has asked me twice in my life what I would like to become or achieve. The first time I answered: a vet. The second time: a professor. I became both. It is important to ask each other questions, and we should do it a lot more, also in science. Bert van Zutphen, Anton Beynen, and Vera Baumans introduced me to the subject of laboratory animal science and taught me how to understand and love it.

Jan Jonker, I have only come across you in the papers and on the Internet, but thank you so much for the terrific idea of a Public Accountability lecture and for setting the example. Joop Koopman and Carel van Os, you have worked hard to create this position for me at Radboudumc. Emile Lohman, chairman of the Board at the time, and Dirk Ruiter, Dean, you made sure our backs were covered when we implemented the many changes we made. Dirk, thank you for seeing me the very same day whenever this was necessary and for arranging matters effectively and efficiently. Janneke Horn, we have only ever been in touch by e-mail, but I would like to thank you profusely for being the first Dutch physician to publish a systematic review of animal experiments. Many people have followed in your tracks, and rightly so. Sir Iain Chalmers feels we should put up a Janneke Horn monument for you, and I support this idea all the way. I like to thank Malcolm Macleod, clinical neurologist from Edinburgh, because it was his lecture that informed and inspired me to change over to systematic reviews of animal experiments. Jeremy Grimshaw, director of Cochrane Canada, invited us to be the first to take part in a Cochrane Collaboration conference. Now we have been given permission to submit an application to be admitted to the Cochrane Collaboration with a laboratory animal working group.

At the time, Gert Jan van der Wilt and Paul Smits integrated our work into the Nijmegen Center for Evidence Based Practice (NCEBP), which sparked many developments. Thanks to Bart Kiemeney, we were also embedded in the new Radboud Institute for Health Sciences (RIHS), and thanks to Wout Feitz in Regenerative Medicine. Many systematic reviews have already been written together with the Surgery Department, and I would like to thank Harry van Goor, Michiel Warlé, and Kees van Laarhoven. Maroeska Rovers, your support, comprehensive knowledge, and great enthusiasm in helping us with your expertise in systematic reviews of clinical studies is invaluable. The way you collaborate with other people is exemplary in this world. Miranda Langendam, our trip to London to achieve a closer collaboration with Malcolm Macleod, Emily Sena, Nathaly Percie and David Howells, was a joy, both in professional and in personal respects. Our collaboration in the worldwide GRADE working group is highly beneficial and productive and will no doubt improve our understanding of how we can achieve better translatability of animal experiments to the clinic.

A phrase that was first launched by Cathy van Beek, animal dignity, has become a fully established term at the CDL. In addition, Cathy arranged for systematic reviews of animal experiments to be included in the sustainability guidelines of Radboudumc, making

Radboudumc unique and a trend-setter. The solid backing by the successive licensees, Roelof de Wijkerslooth, Bas Kortmann, and Gerard Meijer, has been important in being able to steer a straight course amidst waves of clashing interests. You have also underscored that, as a professor, I have my own independent position, which has helped us to keep pursuing high-quality science and human and animal welfare. What would SYRCLE have done without the expert support of Alice Tillema at the medical library. The library staff deserve to be given full credit for their work. Despite the initial scepticism of your manager, Alice, you chose to help us set up our educational programmes. Fantastic! The statistics support provided by Joanna in't Hout is priceless. I greatly value the conversations we have, as you manage to put things in their proper rational perspective. Rob Scholten, director of Cochrane Netherlands, we first met to discuss systematic reviews of animal experiments for the Radbode, and I then tried to convince you that we should join the Cochrane Collaboration. In any case, you have always wished us well and told us that we were heading in the right direction and should persevere. You also predicted that we would be up against a lot of antagonism, as did Cochrane at first. How right you were. We often reiterate your words: 'Keep going, you're on the right track.'

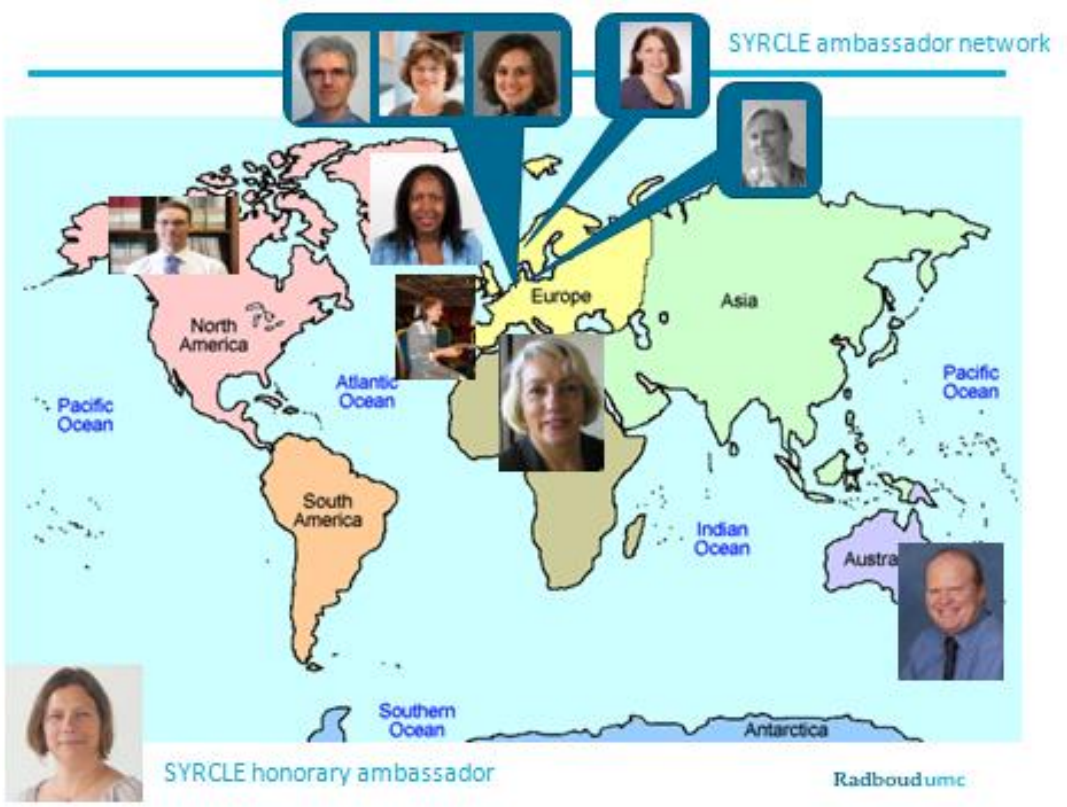
I like to thank my CDL colleagues for the daily effort they make to improve the lives of animals and humans. We are united in our love for animals. We can and shall make a difference. My SYRCLE colleagues Rob de Vries, Carlijn Hooijmans, Marlies Leenaars, Kim Wever, Judith van Luijk, Cathalijn Leenaars, and Miranda van Velzen: without you, we would never have been able to put this issue so firmly on the global map. Our joint idealism, zest for work, and our drive are contagious because we are working towards a better future for animals and humans; we also care to share, getting others to catch the bug and join our important work. My peer-to-peer coaching group, consisting of Professors Olivier Hekster, Marit Monteiro, Peter Jan Schellens, Joep Smeets, Sander Geurts, Klaas Landsman, Anne Speckens, Fred Sweep, and Daniel Wigboldus: I thank you from the bottom of my heart for the wonderful evenings we have up at the faculty club. You have helped me through many a difficult moment with your attentiveness, empathy, and sound advice and with your willingness to share your own case histories. This always helps me to reach a new level of understanding. I also owe a debt of gratitude to Jan Engelen, Cornelie de Jong, and Kees Hagenaar for your sympathetic ear and for your support. Marcel Wortel, like no other you know how to rewrite texts while respecting everyone's integrity. A great gift. I thank Otto Boerman, chairman of the Advisory Council, for the way he chairs the CDL Advisory Council: professionalism, level-headedness, and vigorousness will always bear fruit. As co-pilots in the cockpit, I thank the SYRCLE ambassadors: they have the courage, together with us, to stick their necks out, and I hope many will follow suit. A special word of thanks to Henk Smid and Erica van Oort at ZonMW, always prepared to share their thoughts on how to attain goals. Christine Swankhuizen at Tabula Rasa, thank you for your friendship, for contributing ideas, and for your ability to consider matters with all-round objectivity before coming up with a well-founded judgement. I thank Angelique Nielen and Ingrid Hartgers at the Ministry of Economic Affairs for the strong collaborative ties we have and for facilitating the e-learning module. Rients, your unflagging ability to inspire people to embrace life is incredible. Our trip to the Czech Republic in 2015 gave me renewed energy: to really go for my goal!

All of us, finally, owe an immense debt of gratitude to the laboratory animals who

sacrifice their lives for our health. We owe it to them and to patients – to ourselves, therefore – to achieve optimum quality and results.

To halve the number of laboratory animals, double the quality of studies, and quadruple their translatability to patients at a global level: this is absolutely attainable in the years to come, but, as in the years gone by, it will not take care of itself. We will be needing drastic changes, courage, and policies.

I promise you that, in the next decade as in the past thirty years, I will be doing my utmost to lure first-rate people into the cockpit with me so we know where we are heading and will reach our destination. SYRCLE ambassadors are already very good co-pilots, and I hope many will join them. I know I can count on the full support of my loyal and dedicated staff and many colleagues. Your presence here today, I am sure, also makes me feel supported by all of you. Thank you very much.



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NWO

laboratory animals

Stichting Reinier Post

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