Prof. Dr. E.R. de Kloet

Tussenbalans

Universiteit Leiden

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Address given by

Prof. Dr. E.R. de Kloet

On the occasion of his retirement as head of department and

professor of Medical Pharmacology

at Leiden University

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Universiteit Leiden

Mijnheer de Rector Magnificus, Decaan van het Leids Universitair Medisch Centrum, zeer gewaardeerde toehoorders,

My inaugural address was on November 1, 1991.[1] A few weeks ago, after some searching, I found the text again and I was astounded. Everything we have explored over the past 20 years was already included in that address! However, the 1991 text was much more impressive; perhaps because at that time we were not yet inhibited by the facts.

The title of my inaugural address was: '*Equilibrium in a changing world*'.[1] Meanwhile the world has indeed changed a lot over the past 20 years. We are digitalized and mobile. It's all about hypes and scoring points, euro's and the greenhouse effect. Everybody is incredibly busy. We are stressed, but is that a problem? Stress or coping with challenges is an essential requirement in life which is all to do with adaptation and recovery. Stress gives us the strength to do just a little bit extra; a crisis, that may help to get things back on the rails. Stress is the '*spice of life*'[2], as Selye the discoverer said. It is the key to health and vital ageing. That is what the 1991 address was about. It was also the theme of today's symposium, a fantastic event.

This gives me a chance to thank my colleagues for this wonderful symposium. I have enjoyed every second, but I must make an apology. It is a tradition that an address given from the lectern is in Dutch. It is also without slides, so you are somewhat handicapped both in vision and sound. We have made a translation, though, so you can keep track of the proceedings.

I would also like to express my gratitude that you have made the effort to come here. I would like to thank the guides in my life, the fellow combatants, the followers, and those who have put faith in me, and those who would have liked to do so but could not, or those who could but wouldn't. In short, all of you that did join me and still join me in working on an exciting story in science. Of course my deepest gratitude is for Marian: a fountain of inspiration, a beacon, a 'prachtmens'; and of course to Sybren our son, who has endured 20 years of living with two researchers, an important reason probably for the choice of his academic study, here in Leiden, a university to be proud of!

My address today consists of two parts. First something about the world of stress, how one lands in a job like this, the state of the art and where the science is going. Then, a few words about the life of the professor and his field of science.

Stress in the brain

A very good friend of mine, the recently deceased Seymour (Gig) Levine, a pioneer in stress research, called the definition of stress a futile exercise. '*Stress is' he said 'a composite, multidimensional construct, in which three components interact: the* ***input*** *(the stressor), the* ***processing*** *of the stressful information including the subjective experience and the* ***output****, the stress response, that is the spectrum of physiological and behavioural adaptations to restore homeostasis - the equilibrium of life processes-, which interact via complex self-regulating feedback loops.*[3]

The strongest stressor is: no control, no information to predict ongoing events, but with the uncertain anxious feeling that something bad is going to happen". In fact, it is all about coping, the ability to deal with the stressor. If coping fails stress becomes pathogenic.[2,4] Coping is not only dependent on previous experiences and genetic inputs, on cognitive and environmental inputs, but also on the context around the stressful situation. Such a context is determined according to Lazarus[4] by psychosocial factors such as *control, social position, a safe place and attachment.* If any of these factors is disrupted - loss of dominance, homelessness, expulsion, lack of attachment - the challenge may exceed the coping resources resulting in strong emotional reactions ultimately leading to a condition of chronic stress and enhanced vulnerability to disease.

To understand the reaction to a stressor better, we have studied the action of hormones secreted after the stressful challenge. I will not discuss adrenaline, you know - the hormone that makes the hairs on the back of your neck rise when you're frightened. No, it's all about cortisol secreted from adrenal glands into the bloodstream triggered by the brain. The hormone circulates in the blood and coordinates the function of all tissues and cells in response to the stressor. The hormone also easily penetrates the brain acting precisely in those brain regions that initially triggered the response to the stressor. One area is the amygdala from which fearful emotions and behaviour are triggered in the face of a threat.

Another area targeted by cortisol is the hippocampus, a seahorse-shaped structure that receives particular attention from me. The hippocampus contains a special neural circuit that marks emotional experiences in place and context and stores the memories away in temporal fashion. The stronger the emotion, the stronger the memory. The hippocampus is of great importance for the communication between emotional information from the amygdala and cognitive processes underlying appraisal, dealing with the challenge and storage in the memory occurring elsewhere in the cortex.[5]

Cortisol targets precisely these brain areas that process the emotional and cognitive challenges in life. On the one hand, cortisol promotes emotional arousal, motivational and cognitive processes, but on the other hand it prevents the initial reactions to the stressor from overshooting and becoming damaging themselves. Cortisol acts on the battlefield of emotion and reason, which coincidentally is also the motto of the 435th anniversary of Leiden University, this year.

How did I get caught up in this field?

November 28th 1968 was an important day in my life. After completing my masters degree in chemistry I lost a gamble. The consequence was that not I, but my fellow student Willibrord applied for a much sought after PhD position at the Rudolf Magnus Institute in Utrecht. We had tossed a coin to decide who was going to apply, since we were confident the winner would get the job and indeed that is what happened. Willibrord got the job and I subsequently requested an appointment with Professor David de Wied. I explained that in spite of losing the gamble, I would really like to work under his supervision. "*One moment*", the professor said, and he got on the phone and talked for a while with the Director of Organon at that time, dr Stefan Szpilfogel. When he finished talking David said: '*You can start next Monday, 2nd December at Organon as a PhD student*'. "*Thank you very much professor*", I said politely, unaware of the impending 40 years that would bring me to this address in Leiden.

At Organon Johan van der Vies was my guide. His way of working was characterized by vigour, energy and taking the shortest route from A to B. This proved to be a wise lesson. As a PhD student I had to propose a research plan based on a recent discovery described in *Nature*[6] by Bruce McEwen. This stated that cortisol surprisingly acted in the hippocampus and amygdala, which you may remember are precisely the areas which are of crucial importance for coping with fear, stress and memory performance. Our attitude was '*we can do that better in the Netherlands*' and we took the much more potent synthetic analog of cortisol, dexamethasone. Whatever I tried, this potent compound did not enter the brain. It was only 30 years later that we discovered why: dexamethasone rather than corticosterone is readily pumped out of the brain, dexamethasone can't get in.[7]

Thus I sent a letter to Bruce McEwen in 1970, explaining my desperation in the face of my upcoming failure in science. Bruce wrote back: "*By the way, are you by any chance a brother of Siwo de Kloet, a biochemist now in Tallahassee, Florida?*" Indeed I was, and still am the brother of Siwo, who by the way now owns a biotech company in avian science, avianbiotech.com. It transpired that Bruce had been working as a student with my brother. This exchange of letters eventually led to

a post-doc position. We had two marvellous years at the Rockefeller University in New York, which formed the basis for a longstanding collaboration with Bruce. This coming weekend, for instance, we are going to discuss with Nicole Datson the susceptibility pathways in the hippocampus that were identified using an advanced DNA sequencing approach.[8] Susceptibility pathways are networks of genes that can tip the balance from health to mental disease. I am proud to be one of the sons in the McEwen family; in fact there are already great-grandchildren.

After I returned to the Netherlands, I was appointed at the Rudolf Magnus Institute to work on something else: the neuropeptides, under the inspiring leadership of David de Wied. The 'grand finale' was in 1990: the canary experiment with David, Door and Carel ten Cate. We discovered that with the neuropeptide vasotocin song learning of canaries was promoted - they learned their song faster. For this purpose vasotocin acts in a brain area where still new neurons are being made to enable song learning. This beautiful stereotyped song displayed by the canaries is needed for demarcation of their territory to provide shelter to the canary bride.[9]

This action exerted by vasotocin illustrates how the neuropeptides just as hormones can coordinate in temporal fashion the whole spectrum of socio-sexual behaviours required for adaptation and reproduction from the first social recognition through sexual intercourse to pregnancy and mothering the offspring.[10] It was this type of research where David was at his best. David's humour, and his ability to motivate and stimulate were important to me and while saying this I am also reminded of good friends like Wybren de Jong and Bela Bohus, who passed away far too soon.

In 1990 I was appointed professor in Medical Pharmacology and this gives me an opportunity to thank Douwe Breimer for the time he was my boss, rector and friend. My appointment was settled on 25th January, 1990, the day that the Netherlands was hit by a hurricane. I think most of you may still remember what you were doing at that particular time, using your hippocampus.

20 years in Leiden

In Leiden I decided to focus on the mechanism underlying coping with stress which was actually initiated during my PhD period, but that was kept simmering at the Rudolf Magnus Institute while doing the neuropeptide stuff. I liked the stress topic, but also felt I should have a backup program in Utrecht in case the neuropeptide research didn't work out.

We focused on the question: How is it possible that cortisol, a hormone with such a crucial role in adaptation and health could change from being a protective to a damaging agent? What is the cause? What are the consequences? For this purpose I will just give 5 highlights that illustrate the progress in the field.

1: Cortisol is not only released after stress, but also rhythmically every hour. Those hourly pulses are crucial for maintaining the resilience of cells, tissues, and behaviour in case of an emergency when the hormone suddenly rises after stress. Your cortisol pulse is large in the morning in anticipation of a highly energetic day. Stafford Lightman[11], present here, and his group with whom we collaborate, discovered that this pulsatile rhythm disappears and becomes chaotic in some, but not all, aging individuals marking the reduced ability to deal with challenges as one of the consequences. For medical science a simple lesson: please monitor the ultradian rhythm of cortisol, and reinstate during glucocorticoid therapy the pulsatility for the sake of homeostasis, resilience and mental health. Also, if because of mental disorder cortisol levels are chronically elevated, then not only the normal cortisol level, but also the rhythm can be reinstated with glucocorticoid antagonists.

2: Cortisol activates in the amygdala, hippocampus and part of the cortex two closely related receptor proteins in the cell:

the mineralocorticoid and glucocorticoid receptors; for the '*connaisseur*' MR en de GR.[12] This work, initially inspired while working with Bruce, started at the Rudolf Magnus Institute in the 80's with the help of Win Sutanto, Dick Veldhuis, Anke van Eekelen, Anna Ratka, Hans Reul and many others. The finding was as George Fink pointed out a '*gold mine*'.[13] From that moment it was possible to systematically study, measure and interpret stress effects in the brain. The properties and the precise localization of the receptors provided the criteria for performing experiments from gene to behaviour and beyond.

Before I continue this gives me the chance to highlight that communication in the brain is neuroanatomically determined and electrical. Miklos Palkovits[14] taught me that in order to understand the brain, one needs to know the precise position of nerve cells like a chess player, how they are organized in a network and operate in time, space and context. A hell of a job, but if you like geography and chess, it can be hobby. It was a great help in bridging the gap between cells, brain function and behaviour.

In our behavioural studies, Melly Oitzl discovered that the MR enhances the stress reactivity, which is being terminated by the GR. At the same time coping with the experience is being stored in the memory in preparation for the future. The balance in the two receptor-mediated activities appeared crucial for emotional reactivity and optimal cognitive performance, and hence for coping with challenges. Now some years later the behavioural analysis is much more advanced. For instance the MR controlling stress reactivity, actually has an important influence on processes of appraisal and choice of the behavioural response to deal with a stressor.[15]

The clinical application is obvious: post traumatic stress syndrome - where intrusive memories are part of the disorder - are expected to be manageable using drugs that directly target the stress response system. Hence trials with beta blockers and cortisol antagonists are beginning to be successful provided the drugs are applied in the context of memory performance. Likewise, blockade of an overactive stress system during depression and psychoses is also effective.

3: Cortisol action is complex. Be aware that the receptor is encoded by 1 gene, but occurs in dozens of genetic variants, so-called single nucleotide polymorphisms or SNPs. In addition the receptor is surrounded in the cell by at least a few dozen proteins that in different patterns can enhance or suppress the activity of the receptor in the control of gene expression. Then, there are about 6000 genes that appear responsive under different conditions, experiences and behaviours in response to the environment via cortisol. However, in spite of this enormous potential for diversity in cortisol action, the hormone feeds back on that particular neural circuit that underlies processing of specific stressful information via complementary MR- and GR-mediated responses. This action exerted by cortisol is coordinated with its actions on e.g. energy metabolism, plasticity and other processes, also elsewhere in brain and body in order to promote adaptation to the environment.

Onno Meijer investigates a mechanism that is responsible for specificity in this myriad of cortisol actions, and he found evidence that signalling cascades selective for neuroendocrine regulation can be discriminated from emotional and cognitive processes.[16] A cortisol-like compound devoid of damaging side effects is badly needed, it might very well be possible.

4: The gene variants of the cortisol receptor machinery possibly can be used as biomarkers in predicting how an individual will deal with a stressor, and to what extent vulnerability or resilience is affected. It is a hot area in which the Max Planck Institute for Psychiatry under the leadership of Florian Holsboer, honorary doctor of the University of Leiden, is very successful. They have identified a number of single nucleotide polymorphism's (SNP's) that are very promising for the prediction of successful therapy or vulnerability to

mental disease.[17] It is a privilege to have witnessed how the MPIP developed into one of world's leading research institutes dedicated to mental health. Locally, on a more modest scale Roel de Rijk and his group in collaboration with Frans Zitman's Psychiatry Department have identified a combination of SNPs, a haplotype in the MR that is associated with dispositional optimism, a really interesting finding.[18]

5: Corticosterone and cortisol can program emotional reactivity in developing rodent and primate brains. Normally, in the first days of life the olfactory neurons of a young pup are stimulated to ensure recognition of the mother, but if the pups are separated from the mother for longer periods corticosterone rises and activates in the amygdala fear-motivated and withdrawal behaviour.[19] If prolonged, the anxiety center becomes programmed for the rest of life by likely modifying via epigenetic processes the expression of the receptors for cortisol. You can't say whether this is good or bad. Recently, a prize winning contribution by Danielle Champagne[20] demonstrated that indeed early life programming for enhanced stress reactivity enhances performance in later life under stressful circumstances. In other words it seems metaphorically that a programmed highly reactive stress system is an outstanding asset for the stressful life of a bank manager, mountain climber or skating coach, but disastrous for the dull life of a bureaucrat. The lesson: experiences in early life should preferably match with later life circumstances.

However, '*nothing is written in stone*' was once one of the famous sayings of Gig Levine, and Jonathan Seckl has demonstrated that the senescent brain is plastic in structure and function, for instance by treatment with anti-depressants.[21] In rodents in a special place of the hippocampus, stem cells can generate new neurons, and the group of Erno Vreugdenhil and Carlos Fitzsimons discovered that the integration of these newborn cells into the hippocampal circuitry depends on corticosterone.[22]

In our research we have the great pleasure of a close and fruitful collaboration with the group of Marian Joëls and Henk Karst, currently at the Utrecht Medical Center. Thanks to Marian and Henk we now know much better how glucocorticoids like cortisol and corticosterone act in the brain on cellular excitability. Their most recent discovery revealed that the very same receptors that slowly regulate the transcription of genes, can also promote excitation very quickly.[23] It is a discovery with an enormous impact, because it points to a mechanism explaining how cortisol can promote stress reactions rapidly, which are then slowly suppressed to prevent them from overshooting.

To summarize, I hope to have clarified for you:

Firstly, that coping with stress via study of the action mechanism of cortisol can be measured and interpreted in terms of specific signalling pathways in the brain. Using systems biology approaches in an approach that one could call '*the endgame*' (re: the genome structure is known) in unravelling genes and proteins organized in pathways, a lot can be learned giving the illusion that pathways can be mapped. In my humble opinion a real breakthrough in this timely business is only possible if this unprecedented new systems knowledge is combined with a smart experiment. Such an experiment could take into account that environmental input determines the brain's activity, which in turn provides the context to cells governing the molecular changes we are so fond of. Glucocorticoids power this environmental input from brain to molecule.

Secondly, cortisol signalling is a determining factor in resilience, needed for counteracting chronification of mental and neurodegenerative disorders. Genetic variants seem promising as biomarkers and novel steroid modulators with fewer side effects may very well substantiate personalized medicine in the treatment of stress-related diseases. This is needed more than ever, since depression and anxiety disorders

are estimated to cost 150 billion euro's annually with about 60 million patients, second only to cardiovascular disease.[24]

Thirdly, stress-related brain disorders are characterized by the inability to adapt properly to the outside world. This implies that dysregulation of stress hormone regulation actually impairs adequate processing of environmental information. If stress hormones are dysregulated vulnerability to metabolic, cardiovascular and neurodegenerative diseases is also enhanced. The threat to mental health is most extreme when by damage to the hippocampus adaptation to stress is not possible at all as is perhaps the case in Alzheimer Disease. Medicines capable of preventing or postponing the onset or progression of Alzheimer are urgently needed. Meanwhile, since the patient is incapable of adapting to change, one could say this individual depends on the reverse: adaptation of the environment to the individual during this phase of the lifespan.[25]

The Life of a Professor

In an ideal world research is driven by curiosity. The University creates the conditions for outstanding performance in research and teaching, in the case of the LUMC top research into disease and medicine. A discovery gives a euphoric feeling, the manuscript is easily written and your work is immediately published by a friendly editor in one of the top journals. Funding flows into your laboratory. The university rector and faculty deans carry you through downtown Leiden on their shoulders while singing: '*for he's a jolly good fellow*'.

The reality is not quite the same. A retired colleague of mine, Pieter Smelik[26], noted that the male scientist shows some similarity with a vulcano: if he is slumped in his chair with smoke spiralling upwards (he occasionally takes a cigar from his own box) people say: '*look, he's working*'. But cigar smoking at work is a thing of the past. The scientist these days is a busy little chap: he has meetings all day long, markets science, sells brain work as being relevant for clinics and society, valorises findings, organizes financing for start-ups and manages finance for research. The scientist must publish, but only in journals that have a high impact factor.

These new trends have prompted mixed responses from those who do the work and as an example I quote a fragment from a recent editorial of Alan Fersht in the Proceedings of National Academy of Sciences (PNAS)[27]: '*The terrible legacy of impact factor is that it is being used to evaluate scientists rather than journals, which has become of increasing concern to many of us. But some burocrats want a simple metric. Judgment of individuals is, of course, best done by in-depth analyses by expert scholars in the subject area'. My experience of being on review committees is that more notice is taken of impact factors when the committee members do not have the knowledge to evaluate the science independently'.*

That does not deter from the pleasure of publishing occasionally in Nature or Science, and we are proud when this happens. However, the most innovative findings and breathtaking discoveries are usually in sound author-friendly specialist journals. I suspect by the way that ten years from now the whole hocus-pocus around impact factors will be outdated and that 'data mining' can readily uncover the results of publicly financed research on the internet. Why not, if your mobile phone is already outdated half a year from now? Reputations can then be based once again on real findings and scientific oeuvre.

We have had the fortune to work at the Leiden/Amsterdam Center for Drug Research, a smooth operation thanks to effective management and visionary leadership. More recently, we benefit from the thriving Leiden Institute of Brain and Cognition, and the launching of the Leiden Center for Translational Neuroscience that together with an established Leiden Center for Genome Technology meet each other in at least three University-wide research profile areas. With the Centre of Human Drug Research and the LACDR it is

obvious that the Leiden niche in the national and international neuroscience arena will have a pharma accent integrating technological platforms from cognitive science to imaging and gene technology.

By focusing on research profile areas, education will also benefit. The student can have the opportunity to feel the vibrations of frontline multidisciplinary research, which can then get further emphasis if interaction with mentors is promoted by confrontation. This implies a model in which the student is confronted with tasks and has to demonstrate initiative and cooperation, an approach that appeared successful in the international schools we first organized with William Rostene[28] some 25 years ago, always in secluded Mediterranean locations.

I am proud therefore that the staff of Medical Pharmacology was occasionally awarded the '*best teacher*' award and that in collaboration with Endocrinology and other Departments the course on Hormones and Brain earned the qualification '*best course*' of the year. I wish my colleagues much success in the new minor and master structure of cognitive neurosciences, the biomedical and biopharmaceutical sciences. However, there is one important condition to be fulfilled: the advice of *Franciscus Agricola* who, thanks to my colleague Henk Jan de Jonge, could not have said it better:

'Vacásne parúmper míhi? Resérva áliquid témporis mihi'

or in good Dutch: '*heb je even voor mij? maak wat tijd voor mij vrij?*'

In the past decades we have been supported by the Netherlands Foundation for Scientific Research, the Royal Netherlands Academy of Arts and Sciences, EU programs, Heart Foundation, Brain Foundation, and the International Foundation for Alzheimer Research, Organon, Corcept Therapeutics, and more recently through TI Pharma Lundbeck in Denmark. We are grateful for their support. All of this, of course, could only be possible through the faith in our endeavours by Leiden University Medical Center, also in critical times, and the hospitality and support by the staff of the Gorlaeus Laboratory.

Over the past 20 years hundreds of students, PhD students and post-docs have been guided through our department and steered towards a fantastic career thanks to the tenured staff of about 10 individuals. In this address I have occasionally mentioned someone in particular, but believe me everyone is equally close to my heart, since all the time there has been a friendly, enthusiastic and creative atmosphere. A special word of thanks however I would like to give to Ellen Heidema for her style of personal and management assistance from 1990-2008. Her efficient and warm performance has been quietly continued by Wendy Rodger, a great relief in this complicated time.

To close, the science at the interface of pharmacology, endocrinology and the neurosciences is traditionally strong in the Netherlands as is apparent from the legacy of Ernst Laqueur, Marius Tausk and the Leiden scientists Sam de Jongh and Peter van Rees amalgamated with the ideas of David de Wied. I am proud therefore to wear the toga of my predecessor Sam de Jongh from 1935. In the light of these heroes of the past I realize that the future will be characterized by enormous technical innovations. Naturally, the classical disciplines physiology, endocrinology and pharmacology will always retain their relevance. I quote Marius Tausk at the foundation of the Netherlands Endocrine Society on May 10th, 1947, who stated:
'Endocrinology is a concept, an approach, or even can be considered a method. Whatever the specific endocrine sub-discipline, topic or subject might be, the binding element is the objective, which is the understanding ***how*** *signals coordinate the processes in cells, tissues and organs'.*[29]

In line with this I have substantiated my commitment via teaching and research in the area of neuropsychopharmacology of hormones, this implies how hormones and drugs can affect the brain, in which we define the mind for the sake of convenience as the product of the brain's activity. The neuropharmacology explains how psychotropic drugs act and what their impact is on neuropathology and psychiatric disorders.

Neuropsychopharmacology has a long tradition: already thousands of years ago the Phoenicians used extracts of a Sardinian variant of the Oenanthe Crocata, to get a grin on the face of superfluous 65+ individuals. During the ceremony the drugged pensionado was thrown from a rock into the sea. Louis van Gasteren, the famous moviemaker drew my attention to very recent research showing that the so-called 'Sardonian smile' displayed by the victim during sacrifice was caused by a hallucinogen and a Gaba-ergic blocker inducing convulsions and rigidity of the facial nerve.[30]

The smiling 65-plusser obviously did not return. Ron de Kloet will also not return, but in this case because he is not actually leaving. This gives me the opportunity to thank the Royal Netherlands Academy of Sciences for awarding me the Academy professorship in 2004. The appointment based on this award has been prolonged for a number of years, I suspect because there are no rocks yet in Leiden to finish the job. However, in science the job is never finished, hence time for a moment of relfection, a 'Tussenbalans'.

Ik heb gezegd. I have spoken.

Noten

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1968-1972	PhD research, NV Organon, Oss
1972	PhD University Utrecht
1973-1975	Postdoctoral fellow Rockefeller University, New York City, USA
1975-1990	Associate professor, Rudolf Magnus Institute, Utrecht
1989-1991	Max Planck Institute for Psychiatry
1990-2009	Professor and Head Department of Medical Pharmacology, Leiden/Amsterdam Center for Drug Research, Leiden University Medical Center
1993-1999	Chair Netherlands Society of Endocrinology
1998	European Medal, British Endocrine Society
1998	Emile Kraepelin Guest Professor, Max Planck Institute for Psychiatry, Munich
2001-present	ISIhighlycited.com, one of the 250 most cited neuroscientists
2003-present	Chair Scientific Advisory Board Max Planck Institute for Psychiatry
2003-present	Board Internationale Stichting Alzheimer Onderzoek
2004-present	Academy Professor, Royal Netherlands Academy of Sciences
2005	Geoffrey Harris Prize, European Federation of Endocrine Societies
2007	Annual Award, European College of Neuropsychopharmacology
2008	Lifetime Achievement Award, International Society for Psychoneuroendocrinology
5 March 2010	Farewell address: Tussenbalans

My address given on the occasion of my retirement as professor of Medical Pharmacology describes how I became interested in research on stress in the brain, how a typical career in science proceeds and the highlights celebrated during my career. The objective of this adventure in science was to understand how the stress hormone cortisol can tip the balance from health to disease. What is the cause and what are the consequences? The new knowledge leads to medicines targeting the mechanism of stress adaptation itself to boost resilience and recovery from mental disorders. To achieve this goal an enormous database has been obtained over the past years, but the real breakthrough awaits a smart experiment. Thus, time for reflection, a 'Tussenbalans'.

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