Retrospection to the future

Rector, Chairman of the Board of the Leiden University Medical Centre, Ladies and Gentlemen.
More than 40 years after my first introduction to Neurology and almost 25 years since my appointment as Professor and chairman of the Department, this is a time to reflect and to look at what has changed over that period. What can we learn from the past so that we can carry out our core tasks - those which have been entrusted to us - properly, and also improve our performance? The title of today's symposium: "From bed to bench and back to the future" conveys the essence of the inextricable link between care, research and education, where research is initiated with the patient as starting point, and with the intention to apply the acquired knowledge in the health care sector. Without history, there is no present and no future.

How has care changed?
The most important change over the past 40 years is the development and introduction of many techniques in diagnosis and treatment. The CT Scan, MRI, Immunological and DNA techniques have altered the practice of medicine. Computer technology is at the heart of this development, as well as forming the basis for recording data and for communication, and enabling an acceleration of all processes. Practice has shown that care is not usually prepared for new developments, but has to respond afterwards. Also, society has developed a different view of care, partly because of the wide availability of knowledge. As virtually everything can be found on the internet, there is a need for experts to retain an overview of their diminishing field of expertise. In the last 4 decades, many sub- or super-specializations have developed in Neurology. Many working groups in the Dutch Society for Neurology have their own scientific meetings and have become embedded in global expertise networks. All of this has had implications for care, training and research. There is an automatic compulsion to collaborate, something which has, for some, proved to be a culture shock, but which has resulted in enormous progress.

The main themes which have become important in care, research and education are transparency, responsibility and guideline/direction. Each of these elements actually has some relevance. But it is with application and performance that things often go wrong. Practical experience has convinced me that no-one working in health care intends to deliver poor work which would in some way harm the patient.

How has work changed over time?
With the increase in number of doctors who are not available all the time, do not provide continuity of care, have less experience and who, due to the increase in knowledge and technical options of more specialisms, need to know more in a complex health care organization and work in a 'glass' house, there is a need to develop signposting, directional lines; in short, a need for guidelines. The guideline is a compact document with recommendations for diagnosis and treatment to support healthcare professionals and care users, aimed at improving the quality of care. It is based on scientific research supplemented with expertise and practical experience and is economically justifiable. Some comments to put the practice into perspective are in order here.
In the development of guidelines, the professional was given the task of searching the literature to find as much evidence-based medicine as possible to support the guideline. But how much, for example, is actually known about the effect of medication? A research team from the British Medical Journal examined 2,500 medicines from daily practice to prove the claimed effect. In only 12% did there appear to be sufficient scientific evidence (Clinical Evidence Handbook) (1). Effectiveness was unknown for 49% of the medications. Voltaire's statement: "Doctors put drugs of which they know little into bodies which they know nothing about" is still valid. However, no neurologist will stop prescribing levodopa for Parkinson's disease because no randomized placebo-controlled clinical trial has been performed, and there is no thorough evidence-based medicine evidence by current standards. What proof is needed before being allowed to prescribe a medicine? We must not simply apply the measures of today to the findings of the past. We need to find something between large sponsored multicentre multinational trials with hundreds to thousands of participants looking for statistically significant, but clinically not always relevant results, and small N is 1 studies with individual desired outcomes. The fact that the patient is participating in research already has an important clinical effect. The degree of generalizability of the results of large trials with strict inclusion criteria is overestimated. A possible way to individualize the effect may be by using pharmacogenetics, an area that is still underdeveloped in practice. The involvement of the pharmaceutical industry, although an interested party, is not a problem in itself, provided there are clear agreements and results are always published, whether or not they support the hypothesis. The Neurology initiative(2) to publish a Journal for so-called negative results is very helpful. It is a good step, because most editors of the large journals reject these kinds of studies and thus deprive the community of important factual knowledge. Guidelines only use published literature. Publication bias, therefore, plays a major role in the development of guidelines.

Returning to the intention of the guidelines, which should be short and practical: After months of multidisciplinary meetings, a dementia guideline was created consisting of more than 200 pages. The carpal tunnel syndrome directive ended up as more than 100 pages, but there is a good initiative to shorten it substantially to a few pages, not only after a guideline for creating guidelines was developed: this was 84 pages long.(3)
With the introduction of guidelines, one slightly naïve policy maker suggested that health care would, therefore, become cheaper. If the guideline is followed and unnecessary diagnostics are omitted, and any deviation from it is reasoned, this would certainly be feasible. But in practice a different path was taken: one of completeness, risk-avoidance and defensive behaviour, in which the care recipient plays no small role. This development has resulted in a guideline giving direction and mandatory legislation to the outside world, something that was never the intention.

The quality of the employees must be made demonstrable, meaning that systems are being developed to train, record and test, to inspect or to audit: are these guidelines being applied? The treacherous, dangerous box-ticking system then comes into play. Are all the ticks neatly lined up when the inspector comes along, but as soon as he has gone, the operator reverts to his old habits? One should not underestimate the sense and complexity of an audit, provided the simple quantification of ticks can be omitted. New forms of auditing close to the employee and the recipient of care are steps in the right direction. An audit promotes the awareness process, opens eyes and encourages structural improvements. But the quality has to be in the employee, where the employees and the patient have to decide together how things have gone. Quality of care can partly be seen in the result. But here again, a comment. The individual result cannot be read from a general performance indicator, laid down in a guideline on how to get there. In healthcare, this has to be an individual result per patient. A primary endpoint will have to be determined. The goal will be to help someone; sometimes the person will be cured, but much more often the result is an improvement in quality of life, and sometimes in quality of dying. The guideline must be a helpline, a checklist. Quality of life is subjective and must, therefore, be determined together with the patient. Making the right treatment decision together with the patient is now called "shared decision-making", but this is not new. What is new is that the patient is much better informed and has, therefore, become a better partner in the conversation. Hence, a good treatment can have many outcomes, not only a satisfied patient walking home. In extremo, the death of a patient may be the best and desired outcome of the

treatment, while many actions, many interventions, with the thought that ‘we have done everything we could’, namely carefully followed the guideline, may well be the worst. At the same time the individual variation indicates that the socially anticipated performance indicator may in fact not be unambiguous and as such meaningless. The performance indicator that only deals with the process is not helpful, because accidents also happen on good roads with signposting. The question is how do we drive on those good roads? What training do the users need?

The basis must, therefore, lie in a good education which promotes devoting attention and time to the patient. In practice, one must learn to apply the available knowledge, usually on the basis of guidelines. The street plan and signs have to be learned, especially which traffic rules apply. The neurology is relatively simple; you have to listen carefully and look carefully, obviously with an extensive package of knowledge, broader than just the nervous system, as the core of the human being. This is all included in the training plan for the neurologist, NEURON, although there is also a box-ticking system standing around the corner. . Listening and looking at a patient form the basis. This may sound old-fashioned when all that nice technology is available, but technology is useless if the case history is not recorded properly and there is not enough thinking, bearing in mind the guideline, not to forget anything. Targeted additional research can then be performed. The adage in the department has always been that any additional assessment that is available can be carried out if there is clarity about the problem and about what can be done with the result.

The availability of technology has changed peoples’ attitude. After an hour of questioning and examination in the outpatient department of neurology, the patient goes home with a conclusion and explanation, and may sometimes react: the most technical piece of equipment was the neurologist's lamp; they didn’t even make an MRI . It is clear that there is still work to be done; the neurologist may not have paid enough attention or explained carefully enough. But on the other hand, this also characterizes society’s sacred belief in technology. Society must also learn to deal with the use of technology. The fact that it is available does not guarantee that the patient's problem can be solved, and that health has become enforceable. This social pressure is often used as a justification for behaviour in health care, namely blindly following the guideline: we have done everything we could. Training is, therefore, extremely important. How do we train the doctors and how do we train the specialists? They need to be trained not only to act, to do and how to follow the guideline, but to think and apply a guideline so that they treat the patient. The element of production, number of patients seen, must disappear completely from the

programme and in fact be reduced to real proportions in the care sector in general, resulting automatically in an uncoupling of income and care. In the same mode, attention, looking at and listening to the patients, should receive the highest status and be regarded better than all other forms of diagnostics and therapeutic interventions.

What has been achieved by research?
Over the past decades, progress has been made in the knowledge, treatment and care of virtually all neurological disorders, but today I cannot ignore Huntington's disease, a disorder which I have been working on for many years. One can illustrate a number of developments. First, a brief word about the disease itself. Huntington's disease is a rare inherited disorder with a prevalence of fewer than 10 per 100,000 people. This means that in the Netherlands, there are an estimated 1,700 patients. It is an autosomal-dominant, inherited condition. In every pregnancy, the foetus, regardless of sex, has a 50% chance of inheriting the genetic material from the affected parent. i.e. there are about 9,000 carriers who are at risk of developing the condition. The genetic defect is a CAG repeat extension on the short arm of the fourth chromosome; an apparently useless repetition of a coding piece of DNA. The number of repetitions is on average 17; when this recurrence exceeds 36, it leads to Huntington's disease at some stage of life. The average age at onset is between 30 and 50 years, but the youngest patient I have seen had an onset in the second year, the oldest in the 80th. The clinical characteristics are unwanted movements, resembling dance movements, chorea, and a decrease in spontaneous locomotion with hypokinesia and bradykinesia (decrease and reduction of movement), behavioral changes, increased irritability, depression and anxiety and cognitive decline, dementia. In addition, emaciation and autonomic function failure occur. This is a rather factual summary of an impressive progressive disease that destroys the patient both physically and mentally, eventually resulting in a complete loss of independence. The illness affects the person himself, but also the whole family.
Establishing the genetically based cause in 1993, some 25 years ago, led to a worldwide increase in interest.(4) It was the first brain disease that could be determined with certainty during life, in contrast to the much better known and more common Alzheimer's disease and Parkinson's disease. This finding had three major consequences. First: It posed new questions to society and healthcare, which had not been thought about before. It generated a new demand for care. Not the traditional scenario in healthcare: ‘I have a symptom, what is the cause?’; but ‘my parent is ill, will I become ill later?’. The so-called presymptomatic diagnosis test was set up together with clinical geneticist and

psychologist. Colleague Professor Aad Tibben was a pioneer in this area. The technique was available, but how should it be applied in practice? Although everyone had seen it coming, no-one was prepared for this. On the basis of a guideline developed by the International Research Committee on Huntington's Disease, agreements were reached about the accessibility and supervision of such a project. (5,6)The number of ethical questions did not diminish. How should one deal with available knowledge, who is allowed to use it, will I bring children into the world knowing that they may develop this disease or definitely have it? Which forms of family planning can, may or should be used: primary prevention, no children, chorionic villustest, amniocentesis, and pre-implantation diagnostics, also called embryo selection (PGD). A second example of the technique preceding the social and ethical discussion: How to apply the PGD, who qualifies and who does not? Is it right to do everything or should everything be done becauseit is technically possible. Does a patient have a right to such complex medical intervention? Can anyone derive rights from the fact that it is available, or only if certain conditions are met? How can the newly acquired genetic knowledge be used to prevent the disease? Abuse of genetic knowledge must also be prevented. In the direct diagnostic process, uncertainty can be removed and a direct diagnosis made without extensive additional research. In practice, less than a quarter of those at risk want to find out whether they are carriers of the hereditary material and can pass the disease on to the next generation. Because of the change in the therapeutic landscape, this number is expected to increase.

The second consequence of finding the gene was the start of research worldwide to unravel the mechanism of action of the then unknown protein, huntingtin, translated from the prolonged CAG repeat, with the ultimate goal of developing an intervention, a drug, to at least slow down the process of degradation in the brain or stop it completely. At the same time, techniques became available to make short DNA and RNA strands. You can see where this is going. In simple terms: there is a piece of DNA that is too long. The RNA and protein coded by it are, therefore, also too long. So stick a patch, an antisense oligonucleotide (ASO), on the piece of DNA, or RNA, that is too long so that only the normal non-extended part is read, resulting in a decrease of the too long, pathogenic, protein. In the mouse model with a built-in extended CAG repeat, a so-called Huntington mouse, an antisense oligonuleotide was injected directly into the brain. (7) This caused a reduction in the huntingtin and a mouse that did a little bit better. This was the basis for the first human study conducted by Prof. Sarah Tabrizi in London. In December 2017, the first two relevant data emerged. The agent, introduced into the cerebrospinal fluid by lumbar puncture, prove to be safe and reduced the level of the 'wrong'

huntingtin protein. A wonderful basis for investigating the clinical effect. This will take the form of a worldwide study, using the existing international network. In Europe it will start in mid-2019. Such reports produce strong emotions in the Huntington community; the perception is sometimes that a medicine has been found and should therefore be available. After that December report, many patients registered for the drug or for the study of the effect of the drug. The challenge to the professionals is to manage this properly. Also, the task for the professionals is to think now, and not to be surprised; it is better to start thinking ahead about the next steps should the application of the ASO delay or stabilize the disease process. There is still the opportunity to think ahead and to be better prepared for a number of questions: When should it be applied in a gene carrier, with unpredictable onset of symptoms? Should someone be treated from birth with a possible onset of illness at the age of 40? This would mean that the genetic status of the person is known before the person himself has control over it. Should patients who have progressed far in the disease process be treated and their suffering prolonged? The international network for this discussion is open, both for the effect study and for forward thinking.

Currently, as this hopeful research is evolving, there are patients who need care. Following the example of the Parkinson Network, set up by Prof. Bas Bloem, specialist nursing homes with adapted accommodation units for patients with Huntington's disease have taken the initiative to develop the Care Network Netherlands Huntington. The aim is to widen the knowledge of doctors and paramedics via a national network, so that care for patients can be realized closer to home and be given by well-informed, trained care providers.

A third consequence of finding the gene is the growth in research and international cooperation. In 2017 alone, more than 1,200 articles on Huntington's disease and closely related disorders appeared, a ten-fold increase over the last 40 years. The number of publications is not what it is about; the content determines the importance. The development of the internet, the ability to store and process large data files and the rarity of the disease have facilitated the realization of a worldwide collaboration in the field of Huntington's disease. The basis for this was already laid in 1976, prior to all technical developments, in the report of the Commission for the control of Huntington's disease for the department of health, education, and welfare and the NIH. This Commission was presided over by Marjorie Guthrie, a dancer married to the Huntington patient, Woody Guthrie. The collaboration led to the establishment of the Research Committee on Huntington's Disease of the WFN in 1976. Two of the co-initiators were from Leiden, my predecessor George Bruyn, and the Leiden geneticist Lou Went. It was a unique multidisciplinary

initiative, with participation of patient organizations from the outset. In 1993, the Huntington Study Group was founded in the United States, followed in 2004 in Europe by the EHDN, the European Huntington Disease Network. Both are multidisciplinary professional groups, medical and paramedical, working in close cooperation with the patient associations. A large joint global project has resulted: Enroll-HD, a database, a source of knowledge and a basis for intervention research. This organization would not be able to exist without the huge financial support of the Cure Huntington Disease Initiative.

On the basis of the experience in Huntington's disease, one can illustrate other aspects of development in the field of science.. Increasing scale, demand for transparency and risk-avoiding behaviour unfortunately also contribute to scaling up in the bureaucratic legal field. 40 years ago, a protocol contained the research question, patients and method section, written on a few pages. A current, albeit mostly multicentre protocol, covers more than 100 pages, where the reader has to search for the actual objective. Much more serious, and this applies to all human-bound research, is the fact that the ICF form, the informed consent form, has grown over the past four decades from 1 to 2 pages of comprehensible information about the purpose of the research and the burden that this posed to the participant, to an almost illegible legal document that somewhere contains the facts of the investigation, but that has become a defensive document in the interests of the client. All summarized compactly in 22 closely printed pages. This misses the point for the participant. It creates suspicion rather than giving a clear explanation, so that the participant knows what he is embarking on. Then in practice: Participant looks at the researcher and asks: is this all right? Yes? Where can I sign? In short, there is a task here for the researchers to counteract this. The result is that the participant in the survey is not at all well informed. The main aim of clinical research, to improve care, could be lost and that is the last thing one wants because it is against the patient's interests.
Participation in multicentre multinational research is increasingly becoming a challenge for the researcher. Here, too, it has unfortunately proved necessary to introduce more control mechanisms, but they sometimes also fail to achieve the goal. Of course, the ICF form must be unconditionally signed and present before the study begins. But signing a blank page to confirm that it is empty, and I mean really empty, goes far beyond the limits of reasonableness. Transparency on acquiring the data is necessary. Research must provide evidence of meaningful effect for the patient. Decisions are then taken by governments regarding provision, and later reimbursement by the insurer. The pressure from the patient organizations and the pharmaceutical industry may

become too great for some researchers and policymakers. The financial incentive to deliver the so-called correct, desired data on time can put researchers on the wrong track. The pressure from the industry's shareholders can also become too great. But also the pressure of the academy, the performance, the publication pressure, bearing in mind the career, can become too much. During the audits, the papers must be in order and the impact factors must score well. The box-tickers also come along to check the science. The final phase of research, namely making the data public, has weak spots. There must be positive results, but what are they? These are the results of a well-designed and conducted piece of research: No more and no less. The hypothesis can be confirmed or not. Both are extremely relevant. Nevertheless, far too many research results still disappear in the bottom drawer. I am not going say where this drawer is, but it is plausible that it can be found in the corridors of many parties.
Reporting abuses in the acquisition and / or processing of data, whistle-blowing, has, after a few embarrassing revelations, led to these issues being addressed, and confidential advisors and academic integrity committees being set up; unfortunately they do have work to do. The publication of the findings of these committees is intended to have a preventive effect and a lowering of the threshold for those who detect an irregularity. It is often the youngest researcher who notices the irregularity, and it is important to protect that young researcher when the facts become public. The beginning of their career is at stake.

Of the many developments in neurology, the policy for patients with a cerebrovascular disorder has changed the most drastically with regard to the organization of care outside and within the hospital. The work-up changed from static into dynamic. Stroke is the most common acute condition encountered by the neurologist. Annually, 43,000 people in the Netherlands suffer from stroke, 117 people per day, 26 of whom die. Every year there is an additional number of approximately 32,000 people with residual symptoms of stroke; there are about 320,000 people currently living with the consequences of a stroke. My first patient as resident in Neurology was Mr. I. A Hindu, he was adipose with diabetes mellitus and hypertension. He was admitted with a slight skill disorder in his right hand. At the ward round the next morning, he was found to have complete aphasia and hemiplegia on the right. This never improved and he spent the rest of his life in the nursing home. How should this disorder be treated when primary prevention is no longer relevant? The effect of aspirin was already described in 1972 (8), but it took until the eighties for it to become standard prophylaxis in practice.

In the acute phase, after the ECASS study (9), published in 1995, intravenous thrombolysis was introduced in practice and in 2014, after the Mr. Clean study (10), the intra-arterial thrombectomy. Raising awareness among doctors and patients has meant that, on average, the patient arrives at the hospital sooner and streamlined care paths have been created to ensure optimal admission to a stroke unit. What are the consequences? A lower mortality at 30 days, 1 and 5 years after the accident, a shorter admission duration for the patient since the year 2000. But what is the real cause? The general mortality from stroke had been showing a steady decline since 1980; the design of the stroke unit with targeted care and prevention of complications has demonstrably led to a better recovery for the patient; people have become aware of the fact that a hospital is a dangerous environment and therefore a short stay is desirable; the influence politicians and insurers have on expensive hospitalization is considerable. Hence, a combination of many factors has definitely improved the care for these patients. Again, unfortunately, questions often have to be answered afterwards because the individual variation is no less than for a rare disorder. Should every patient be given the same platelet inhibitor after a TIA, while it is known that there are genetic differences in processing the medication, and so this medication does not work at all for some people? Should every patient with a stroke, regardless of current functioning, receive intravenous and possibly intra-arterial thrombolysis? Can the economic consequences of all these actions be borne? On the basis of which information do we take decisions, or advise the policy makers? Is the general outcome measure ‘mortality’ the correct measure for healthcare? Living longer with a disability is not the desired quality of life for all patients. It is important that the neurologist in training gains knowledge about the later consequences of stroke and all possible actions. A part-time internship in a nursing home should be part of the course so that they can see the consequences of their own actions. There is no right to thrombolysis, regardless of what is stated in a guideline. The fact that we are dealing with the application of options for the individual patient definitely applies here. This can sometimes lead to unpleasant situations, when family and doctors disagree. Then the tendency to act often has the upper hand in order to avoid that discussion at the acute moment. The risk of ‘we have done everything’, acted, is a life-sized pitfall, but the patient has not been treated. There is an important role for the neurologist here.

Education

Education plays a major role in all aspects of healthcare and research. Our university, which started as an educational institution in 1575, has grown into a

pure research institute in the perception of many. Research in the medical faculty has its basis in healthcare with the aim of innovation and improvement of care. With the increased development in technology and the extensiveness of knowledge, a further specialization arises, which is important for research and patients. In order to provide up-to-date education, research is, therefore, necessary, not directly into forms of education, but into content. For the motivated student, the form of education does not matter. He has to show that he can jump over a high bar, which can even be raised a little. The number of hours of study which the Dutch student is expected to follow is still low compared to other countries.
Education is an integral part of the academic's duties. As well as cultivating new talent, education is strongly connected to care. Giving explanations to the patient is of crucial importance. You have to be on top of the material to be able to apply the knowledge at the right level and to share it with the patient and family. Yet the value of teaching is underestimated. The trend towards more attention for education must be continued.

To conclude.
Of course, this is only a fraction of all changes that have occurred over the last 40 years. Much more has changed in society and the entire field of health care. At the time of my appointment, I was told that a time would come for staring out of the window, time to think, not being consumed by the issues of the day. A day, a month, a year to take some rest and flee from hectic everyday life should be structurally built into the academic world. Having arrived at the end of my career, that day will come.
Now, I would like to close my public lecture with a few words of thanks. First of all, I would like to thank the successive chairmen of the LUMC Board of Directors for their confidence, Prof Onno Buruma, later succeeded by Prof. Ferry Breedveld and Prof. Willy Spaan. The staff of the Department of Neurology who have grown hugely in quantity and especially quality. Through your efforts, the department has become what it is in healthcare, research and education. The future with all new developments can be met with confidence with Prof. Jan Verschuuren in the lead. All residents, assistants, PhD students, and students who, perhaps not always visibly, have given me a lot of fun and satisfaction; have contributed to the success. I am indebted to all those employees who make it possible to work in the LUMC, the nursing staff and all support services in the divisions and beyond. Thanks especially to the many patients who trusted me. I learned the most about illness and life from them. I could not have carried out my work at the LUMC without the unwavering support of my secretary, Huiberti Belier. I owe a great deal of gratitude to my

family for the space I have been given all these years, at times at their expense. I have said.

Raymund AC Roos
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