H.G.J.M. Kuypers *1925-1989*

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L.C.M. Moll

When Hans Kuypers died in Cambridge,U.K., at the age of he was an internationally renowned neuroscientist, who left an impressive list of papers, many of which are frequently cited, the last of which was published posthumously in .

Figure .
H.G.J.M. Kuypers.

Biography and scientific contributions

Born on September , , in Rotterdam, as the only child of upper middle class parents, he passed through high school ('Gymnasium') there, with interruptions due to wartime circumstances. After his final examination in , he began studying medicine at Leiden the same year. During his medical studies he worked from tot as a student assistant in neuroanatomy and histology under prof. S.T. Bok, who would later be the supervisor for his doctorate thesis. It was here that Hans Kuypers became impressed by the teaching of the neuranatomist Walle Nauta (-), so much so that during his subsequent summer holidays he visited Nauta twice in Zürich to learn the optimal staining methods for identifying degenerating axons. Later in Zürich Nauta developed the silver impregnation technique, which still bears his name as the Nauta method, by which degenerating axons and normal fibres could be more clearly distinguished from each other than by the older methods (Lemon).

Meanwhile Hans Kuypers finished his doctoral work in Leiden, and in he defended his doctoral Ph.D. thesis *Fibre connections of the midbrain central grey* (supervisor Prof. S.T. Bok, advisor W.J.H. Nauta). After two years of internships in various hospitals he graduated as a Medical Doctor (MD) in . In that same year he married Maria (Toetie) Schaap, a technician in the hospital lab. The marriage was blessed with six children, two sons and four daughters.

Wishing to become a neurosurgeon, he moved to Groningen to take up a residency in the neurological department of Prof. J. Droogleever Fortuyn, a clinical neurologist with a strong affinity to neurophysiology and neuroanatomy. "The clinical work however did not stimulate his mind" (Phillips and Guillery), and a year later, in , he accepted a position of Assistant Professor of Anatomy at the University of Maryland, Baltimore, probably helped by the influence of Nauta, who by this time worked in nearby Washington DC.

THE TIME IN MARYLAND AND CLEVELAND USA

In Maryland, Hans Kuypers started a most fertile line of research into the anatomy of movement, linking morphology to function. In studies of cortical connections to the brainstem, he found, among other things, that the motor cortex also receives ascending fibres, e.g., from sensory nuclei in the brainstem and in the spinal cord. Moreover, the post-central sensory cortex not only receives fibres from, but also sends fibres to sensory nuclei as well as to the ventral horn of the spinal cord, both serving as feedback systems (Kuypers). It was Hans Kuypers who unequivocally showed that the pyramidal tract originates not only from the primary motor cortex but from many cortical areas, and that it also conveys 'sensory' fibres (Richard Passingham, Oxford, UK, personal communication). After these studies he gradually came to realise that the motor capacities of the various descending fibre systems are determined not by their areas of origin but rather by their termination areas in the brainstem and the spinal cord, i.e., by the interneurons and the motoneurons upon which these descending fibre systems converge. Therefore, studies of the organisation of the motor system were begun on the level of the spinal cord and in a series of subsequent studies he systematically worked his way up, so to speak. In these studies Hans Kuypers made the most of the advantages of the Nauta method and later of tracer methods using axonal transport, which were developed in the late s and early s (*vide infra*).

He firmly established that there are two descending brainstem systems, terminating in the intermediate zone of the spinal ventral horns: a *medial brainstem pathway* ending mainly in the ventromedial parts of the spinal intermediate zone bilaterally, which are mostly connected to motoneurons of axial and of proximal limbgirdle muscles; and a *lateral brainstem pathway* (for the greater part consisting of the rubrospinal tract), terminating in the dorsolateral part of the intermediate zone from where fibres reach motoneurons of limb and distal extremity muscles, mainly contralaterally. These anatomical data suggest that the medial pathway primarily subserves the guidance of axial and proximal extremity movements bilaterally, and that the lateral pathway is mainly concerned with distal movements and this only contralaterally. In addition to the fibres from these (*subcortical) brainstem pathways* to the spinal motor apparatus there were of course the already well-established *cortical* connections to the spinal cord. These *corticospinal fibres* appeared to be distributed to the same areas of the spinal intermediate zone, as are the brainstem pathways: to the dorsolateral part contralaterally, but bilaterally to the ventromedial parts. Moreover, in the monkey direct corticomotoneuron connections exist, making direct monosynaptic connections with motoneurons of distal extremity muscles (summaries in Kuypers and Kuypers). These direct cortico-motoneuronal connections are found especially in primates with the capacity to execute independent skilful hand and finger movements. These direct connections do not exist, for example, in the cat and are not yet developed in the infant monkey, which is not yet able to move its fingers independently (Kuypers).

These studies, initiated in Maryland, were continued in Cleveland where Kuypers was appointed Associate Professor in the Anatomy department of Western Reserve University in . He now had a family with four young children and "was by now a well-established figure, recognised as an authority on the Nauta method, which many neuroanatomists in the United States considered as extremely difficult to use" (Phillips and Guillery). In Cleveland, and together with Don Lawrence, a neurology resident, he set up a series of investigations into the functional correlates of his anatomical observations.

In the monkey, the descending tracts were transsected each separately or in combination. When the corticospinal (pyramidal) tracts were interrupted bilaterally, the animals were still able to make a whole range of movements after recovery: they could walk, run, climb, jump, and grasp branches and food morsels, but they could not make relatively independent finger movements. They could not, for instance, extract morsels of food out of a small well with their index finger, and this motor deficit persisted throughout the rest of their lives. In another set of experiments, the lateral brainstem pathways and in still others the medial brainstem tracts were interrupted in already pyramidotomized animals. As expected, these experiments showed that the ventromedial brainstem pathways subserve the regulation of whole body and integrated limb-body movements as well as maintaining posture, whereas the lateral brainstem pathway provides the capacity for individual extremity movements, especially of its distal parts. Moreover, the corticospinal tract, and in particular the direct corticomotoneuronal pathway, appeared indispensible for the execution of highly skilled and relatively independent hand and finger movements (Lawrence and Kuypers a,b).

Being interested in the *guidance* of movement, in particular of distal hand and finger movements, which occurs either by way of somatosensory or by way of visual stimuli, Kuypers had also turned his attention to the cortico-cortical connections from visual and somatosensory cortices to the frontal cortical areas concerned with movement. He had already started these studies in Maryland with Mortimer Mishkin, and they were later elaborated in Cleveland with Deepak Pandya. Taken together these studies showed that the fibres from many other parts of the cortex, in particular from 'visual' cortical areas, converge in the premotor cortex and project from there 'back' to the primary motor cortex from where the direct corticomotoneuronal tract originates (Pandya and Kuypers).

THE YEARS IN ROTTERDAM

In , the first Dean of the Rotterdam Medical School, A. Querido, professor of internal medicine, persuaded Hans Kuypers to return to Rotterdam to become professor of Anatomy at the new Medical School (which later, in , merged with other faculties to become the Erasmus University Rotterdam). He was one of a small group of professors, who were asked, "to build a school that would be free of the constraints and traditions of the past" (Phillips and Guillery). Two professors of anatomy

were appointed. Kuypers would teach neuroanatomy and the anatomy of the head and neck. The other professor, H. Moll, would be responsible for the anatomy of the rest of the body. Here, within just a few years, Kuypers built up a truly international department with sections in experimental psychology (with David Hopkins from Canada), neurophysiology (with Simon Miller and later Roger Lemon both from the U.K.), and neuroanatomy (with Don Lawrence from Canada). Under their supervision young students and physicians prepared their doctoral theses on parts of the lab's research line as devised mainly by Kuypers.

The earlier studies on the anatomy of movement were extended. In a clever and surgically difficult set of behavioural experiments in split-brain monkeys (in whom all the commissures had been transsected), Cobie Brinkman and Kuypers obtained strong evidence that in the monkey each cerebral hemisphere steers relatively independent finger movements, e.g., leading to a precision grip only contralaterally, while reaching movements of the arm as well as grasping finger movements (power grip movements) can also be guided by the ipsilateral hemisphere (Brinkman and Kuypers). Subsequently with Rob Haaxma and later with the present author, again in split-brain monkeys, the cortico-cortical pathways possibly subserving the visual guidance of relatively independent hand and finger movements were disconnected and the effects were studied. It appeared that the capacity to execute visually guided highly skilled fine hand and finger movements depends on the integrity of the contralateral cortico-cortical occipito-frontal connections, and that the premotor cortex plays an important part in this respect (Haaxma and Kuypers , Moll and Kuypers). Subcortical structures, such as (on the 'visual' side) the superior colliculus or (on the 'motor'side) the ventrolateral thalamic nucleus seemed to play only a minor role in these evolutionary late developed capacities as are the independent finger movements. Later, with Roger Lemon and Moshe Godschalk, the behavioural characteristics of monkey premotor and precentral neurons before and during visually guided hand and finger movements were recorded. Cells in the premotor cortex appeared to respond during the time that the reward was visible but not during the movement itself, while cells in the motor cortex responded only during the actual movement. The logical conclusion emerged that the premotor cortex was concerned "with recording the position of reachable objects, information that could then be transmitted to the motor cortex for execution" (Godschalk et al. , Godschalk et al. , cited in Phillips and Guillery).

After his wife lost her life in a car accident in Hans Kuypers spent more time on his six children, the youngest being only nine years of age. But in spite of this terrible loss, the flow of papers published by him and his co-workers continued.

From the beginning of his scientific career Hans Kuypers had been fascinated by staining methods and was always trying to improve them. He was quick to embrace new techniques. In particular the techniques that made use of axonal transport, developed in the late s and early s, were promising and he published many anatomical studies on the technique of and the results with the anterograde transport of radioactive labelled aminoacids and later the retrograde transport of the

enzyme horseradish peroxidase (Dekker and Kuypers , Kievit and Kuypers). Later, he developed and perfected retrograde double labelling methods with fluorescent markers (Kuypers and Huisman). These methods revolutionised the research in neuroanatomy as they brought faster and more explicit results with new insights into the wiring of the central nervous system.

THE CAMBRIDGE YEARS

During his years in Rotterdam, Kuypers often felt restrained and even opposed by the University's administrative body. So much so that, in , he took the oportunity to move to Cambridge in England where he was appointed professor and chairman of Anatomy. As his youngest daughter was only at the time, she went with him. Despite a serious heart condition – he had suffered a heart attack not long before – "he threw himself energetically into the reorganisation and rejuvenation of the department, being regarded by some as a bull in a china shop" (Phillips and Guillery). Within a short time he had reorganised and extended the department, and modernised the teaching of anatomy with links to the clinic. He now mainly devoted his research to the development of yet another neuroanatomical tracer. This time it was a virus, the herpes simplex virus, which was known to be transported along nerve fibres, but also across synapses (Kuypers and Ugolini). He came close to achieving his ideal, which was to trace the motor system from the muscles or motor nerves all the way back to the cells of origin in the motor cortex. The task was actually more difficult than it had appeared at first sight. Before this work was accomplished Hans Kuypers died in his sleep on September , , in Cambridge.

The person

Hans Kuypers was a man of strong convictions, determined to reach his goals, obsessed by his desire to clarify the hodology of what Sherrington so aptly called the 'enchanted loom', dedicated to his work, his team and his family (in variable order according to circumstance). He could be stubborn and proud and was not always capable of compromise. He took disappointments and personal blows with much courage. The death of his wife was a very severe blow, leaving him to look after his six children, aged between and . I remember vividly his wife's funeral: Kuypers standing at the grave with his six children in line next to him, giving the impression: "I promise you, we'll make it." Many female housekeepers were successively hired and fired, occasionally within weeks, when their work was not entirely to his satisfaction (Paul Kuypers, personal communication).

Kuypers was a hard worker, being nearly always in the lab on Saturdays, and so were we! Asking for a day off came close to an indecent proposal. When he suffered his first heart attack in the early s, he was admitted to the University Hospital Dijkzigt, which is connected to the medical faculty building where he had his lab on

the th floor. Two or three days later, whilst still admitted, I met him in his pyjamas in the lift on his way to the department. He strived for perfection although he knew its limits and could also suddenly say: okay, this is not perfect but it is good enough. He was invariably willing and available to solve problems and the door of his office was nearly always left open so that everybody of his team, even the youngest technician, felt free to enter with questions or suggestions. The atmosphere of the department in Rotterdam was truly international, the language being a curious mixture of English and Dutch. This was partly since the foreign co-workers did their best to speak some Dutch but also because of the many visitors from abroad, almost on a weekly basis, some staying for their sabbatical and most of whom lectured on their research. I was particularly impressed by the visit of Norman Geschwind (-) with his elucidating views on the disconnection syndromes in animals and men.

Kuypers often had arguments with the University's administrators. When he told the managing board that he was thinking of leaving for Cambridge if his requirements were not met, he was furious but also utterly surprised when they let him go.

As an eminent professional many prizes and awards came his way, and he was elected by quite a number of professional societies. Already in his student years in Leiden he was recognised as a man of strong leadership, being elected president (praeses) of the Catholic Student Association 'Sanctus Augustinus'. He was an excellent teacher and he was very proud when his students awarded him the teaching prize. He received the Winkler Prize for Neurology of the Netherlands Society of Neurology in , and was awarded the Research Prize of the Dutch Federation of Medical and Biological Societies in . He was elected member of the Royal Dutch Academy of Sciences in . He was one of the founding members of the European Neuroscience Association (ENA) and served as its President in the early s. In he became a Fellow of the Royal Society.

After his death in Cambridge, his body was returned to the Netherlands, and he was buried next to his wife in Rotterdam. Two "Kuypers Memorial Lectures" were held in London, UK; the first bij Peter Strick from Pittsburgh, the second bij Gert Holstege from Groningen on the emotional motor system. Two workshops of the ENA were held in his remembrance, one in Stockholm in entitled 'new methods for tracing neuroanatomical connections', and one in Cambridge in on motor systems.

Acknowledgements

While writing these biographical notes I realised again the privilege I have had of working under Hans Kuypers' supervision. Fortunately I could rely on the personal and biographical records of Lemon ( ) and on the detailed biography by Phillips and Guillery ( ). Eddy Dalm sought for and found the photographical picture. Furthermore, talks and correspondence with Rob Haaxma, Gert Holstege, Dave Hopkins, Paul Kuypers, Roger Lemon and Dick Passingham revived old memories, yielded sometimes unexpected facts or anecdotes, and renewed personal relationships.

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