R. Magnus *1873-1927*

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P. Eling*

Figure .
R. Magnus.

Rudolf Magnus, born on September , , was the elder of two children born to the lawyer Otto Magnus and his wife Sophie Magnus Isler. They lived, apparently in fairly wealthy circumstances, in Brunswick (Germany). Diaries from Magnus's mother and grandmother reveal that he was a remarkable child, intensely interested in dissecting his toy animals. Following the Gymnasium, Magnus originally planned to study philology. A friend of the family, professor Richard Meyer, a chemist, convinced him that science would be a far better choice. And so Magnus went to study medicine in Heidelberg in May . Among his teachers figure the physiologist Wilhelm Kühne, the neurologist Wilhelm Erb, Emil Kraepelin for clinical psychiatry, and R. Gottlieb for pharmacology and physiological chemistry. His preserved lecture notes testify to his special interest in neurology. He himself indicated that the lectures and laboratory work with Wilhelm Kühne (-) were of decisive influence.

Magnus performed his first scientific study under Kühne. It concerned a new method for measuring blood pressure from the exposed carotid artery in animals. This method of direct measurement was also the topic of his first conference paper, which he presented at the rd International Physiological Congress in Bern, in . It also was the subject of his doctorate thesis ('Über die Messung des Blutdrucks mit dem Sphygmographen' [On measuring the blood pressure with a sphygmograph]; *summa cum laude*), which he wrote under Kühne's supervision in . Magnus developed a method to record blood pressure directly from the exposed artery, in order to prevent some pitfalls, inherent to other methods, using air or fluid transmission. This was the first of a series of methods introduced or refined by Magnus. Probably the best known of them is the recording of muscle contraction of isolated parts of the feline ileum in a physiological salt solution.

Having completed the medical studies, he went to England for a study trip of approximately five weeks. The main purpose of the journey was to attend the th Congress of Physiologists at Cambridge. He also used the opportunity to travel in England and on his way home, he visited Holland. He presented a paper on the neurogenic origin of the pupillary reflex of the eel and the frog. The question was whether the eye's pupillary reaction to light in fish was due to direct sensitivity of the pigmented musculature of the iris, or to the participation of nervous elements in the iris. This latter position was defended by Magnus.

Confronted with the choice between clinical work and science, he opted for the latter. At the end of , he was appointed assistant to his former teacher, Gottlieb (who was married to one of Kühne's daughters), head of the Pharmacological Institute in Heidelberg. He became 'privat Dozent' at the University of Heidelberg in . Being convinced that he had acquired a stable position, Magnus married Gertraud (Traudl) Rau in February . He probably met his wife in Munich where she practiced painting while Magnus was drafted for service in the Bavarian army. Although both came from a liberal Jewish family, they had been baptised a few years earlier. She was an active member of the liberal Protestant community, while Rudolf was not religious. While living in Heidelberg, they had three children: Karl ( ), Margarethe (Gretl,) and Dorothea (Dorle,). Later, while living in Utrecht (the Netherlands), another two children were born, Erika ( ) and Otto ( ).

Magnus was appointed extraordinary professor of pharmacology in Heidelberg in . During the period - , Magnus produced over articles on a variety of pharmacological and physiological topics. His early studies had convinced him that an isolated surviving organ can serve as an ideal model to study both its physiology and pharmacology. He considered his studies on the small intestine as the most important of that period. One of the papers concerned pharmacological experiments on the *Sipunculus nudus*, a wormlike animal that had been investigated extensively by his study friend Jakob von Uexküll. The segmental structure of its intestine made, for the first time, examination possible of the effects of different pharmacological agents on the intestinal nervous centres, local nerve reflexes, peristaltic rhythm, and the smooth muscle fibres. He showed that the amount the intestinal muscle layer was stretched determined the direction of stimulus-conduction. At international physiological conferences, he met other scientists, whom he visited at later dates, for instance Schäfer (later: Sharpey- Schäfer), Langley and Sherrington.

Magnus spent seven weeks in Schäfer's laboratory in Edinburgh in , and two series of experiments were carried out. The first one addressed the question whether the vagus nerve contained motor fibres for the spleen. Their experiments on a dog, a cat, a rabbit and a monkey indicated that the answer was negative. The second series of experiments revealed that pituitary extracts produced a rise of blood pressure by contracting the systemic arterioles. Magnus and Langley worked in Cambridge, presumably during the Easter holiday , on movements of the intestine before and after section of the mesenteric nerves. They found that after degeneration of nearly all of the post-ganglionic sympathetic fibres, the Auerbach plexus retained all its functions. Magnus's visit to Sherrington in Liverpool in turned out to be a decisive experience, as it formed the impetus for his work on postural reflexes, which became the central topic of his research in Utrecht. His goal for that trip was to start research on the question whether a rule, established by his friend von Uexküll for invertebrates, namely that excitation of a nervous centre tends to spread to stretched muscles rather than to relaxed muscles, would be valid for mammals as well.

In addition to physiological work, Magnus, together with his friends von Domaszewski and von Uexküll, became engrossed in Goethe's scientific papers. This

is not really surprising, since he originally planned to study literature and admired Goethe. Using Goethe's instruments he replicated his experiments in the Goethehaus in Weimar, especially those on colour perception, although Goethe's other work, e.g., on comparative anatomy and botany impressed as well as inspired Magnus. In a series of ten lectures, published as *Goethe als Naturforscher* (translated as Goethe as a Scientist,), Magnus demonstrated that Goethe's observations were correct, but the conclusions drawn from them were wrong.

On his return from Liverpool, a letter awaited him, confirming his appointment to the chair of 'Pharmacagnosis and Pharmacodynamics' at the faculty of medicine of the University of Utrecht. This was the first professorship to be given in pharmacology in the Netherlands. He accepted the chair with an inaugural lecture on September on 'Ziele und Aufgaben des pharmakologische Unterrichts' [Objectives and tasks of teaching pharmacology], arguing that its central task is the study of the effects of chemical substances on the organism. Pharmacology, therefore, is closely connected with physiology and experimental pathology, sharing its methodology with physiology.

Initially, the start of World War I did not affect Magnus particularly. The Netherlands remained neutral. However, in Magnus was called for military service in the German army. At first, he worked as a medical officer in hospitals in Speyer and Mannheim. Later, he was sent to the 'Kaiser Wilhelm Institut' in Berlin, where he investigated, together with Laqueur, the pharmacology of war gases. When the Dutch government informed him that it would have to appoint someone else if Magnus did not return, he obtained permission from the German authorities to return to Utrecht in . He resumed work in the laboratory in a centuries-old building, the 'Leeuwenbergh', together with his co-workers, in particular Adriaan De Kleyn (-), who cooperated in the experiments on postural reflexes. De Kleyn had studied medicine in Utrecht and settled as oto-rhino-laryngologist there. An essential part of Magnus's experiments involved operations on the labyrinth, and so De Kleyn had become assistant to Magnus in . Their cooperation evolved into a close friendship. Magnus and De Kleyn developed elaborate systems to describe the various postural reflexes. Among these were the Magnus-De Kleyn reflexes, which can also be demonstrated in certain human patients. Experiments were also carried out to investigate the effects of pharmaca on postural reflexes. Other co-workers in this area of research were Willem Storm van Leeuwen (-), who was involved in several pharmacological studies, and Gijsbertus Rademaker (-), who worked on a voluntary basis and mainly analysed the involvement of midbrain structures in postural reflexes. Magnus generally wrote the review papers of this work himself. Joannes G. Dusser de Barenne (-) assisted Magnus, at first on a voluntary basis; later he worked with De Kleyn.

The studies on postural reflexes ('Körperstellung') formed the major part of Magnus's work in Utrecht. Many were published in a series of articles on 'Beiträge zur Pharmakologie der Körperstellung und der Labyrinth Reflexe' [Contributions of Body Posture and Labryinth Reflexes to Pharmacology] and subsequently in the monumental monograph on *Körperstellung* (Body Posture,). A Russian translation of this book appeared in , and an English version in . Magnus summarised the

results in the Croonian Lectures, read before the Royal Society in London, .

Magnus also developed other lines of research. One such line was started in Utrecht about , together with his assistant, the chemist Joan Willem le Heux (-). The latter isolated choline as the chemical substance involved in the occurrence of rhythmic intestinal movements. These studies were summarised in the second Lane lecture at Stanford University, San Francisco on 'choline as an intestinal hormone'. Another series of experiments addressed the effects of digitalis on the dynamics of the heart and blood circulation. A minor topic formed the studies on the pathophysiology and pharmacology of the lungs.

Magnus was also interested in the philosophical background of his work. He adhered to the Kantian framework and believed that we use a number of a priori categories such as time and space to perceive the world. These categories have their basis in physiological processes. This point of view is closely related to Johannes Müller's thesis that the different sensory systems are triggered by specific forms of energies. The fundamental role of space can be observed in changes in eye-position following changes in the position and movements of the head in various animals. Together with De Kleyn, Magnus studied this complicated system (which functions already at a very young age, before the eyes are open) in the rabbit and other mammals. Magnus therefore regarded it as a physiological a priori.

After the war, Magnus' workload increased steadily. He became engaged in the development of materials for teaching pharmacology. He was also involved in the foundation of the 'Rijksinstituut voor Pharmaco-therapeutisch onderzoek' (RIPTO, Governmental Institute for Pharmaco-Therapeutical Research), whose task was to determine the biological standard for drugs that were in use and for the evaluation of new drugs. As a result, he was asked to become a member of a committee for developing an International Standard for Digitalis.

The conditions of his laboratory were not adequate to encompass all these new developments in his work and after a number of unsuccessful attempts to get a new laboratory, Magnus was offered the opportunity to develop plans for a new building. Much time and effort was invested in this project in the period between and (see below).

In July he went to his beloved Pontresina, to prepare the 'Lane Lectures' series for at the Stanford University. After a walk, he fell ill and in the subsequent night of to July he died, probably due to a cardiac infarction.

Körperstellung (body posture)

Magnus was intrigued by the finding of his friend von Uexküll, that a stimulus on the central nerve ring had a different effect on the muscles of an isolated arm, depending on whether it is in the resting position or bent sidewards. The underlying principle seemed to be that excitation always flows towards the stretched muscles. Magnus realised that this principle might explain the influence of body position on the pre-

cise form of a reaction to a stimulus. Moreover, Magnus estimated that Sherrington's experience with the study of reflexes in spinal, decerebrated and mesencephalic animals could be valuable for exploring this issue further. Magnus observed in his first experiments on spinal dogs in Liverpool in , that when the knee jerk reflex was elicited on one side, the effect on the contralateral side depended on whether the leg on that side was bent or extended. Magnus developed a research programme in Utrecht, examining posture in a very systematic way. He distinguished between a static and a dynamic (stato-kinetic reflexes) condition, and examined two kinds of reflex mechanisms, neck reflexes and labyrinth reflexes (otoliths and semicircular canal). He eliminated the influence of each of these by sectioning nerves, centrifugalisation (detaching the otolithic membranes but leaving the canals intact) and by lesioning above or below the thalamus, mesencephalon and the medulla. He used cinematography and stereography to register and document the observed reflexes.

The study of postural reflexes addressed four different issues:

- reflex-standing: muscles sustaining the standing (upright) position should have, by reflex action, a certain degree of enduring tone to prevent the body from falling;
- normal distribution of tone: not just the 'standing muscles' but also the antagonists possess tone, and there should be a balance between these two sets of muscles;
- attitude: the position of different body parts must harmonise with each other;
- righting function: a series of reflexes are evoked to return to a normal position when the body is brought out of the normal resting position.

Magnus maintained that the main centres for these functions are located in the brainstem (fig.).

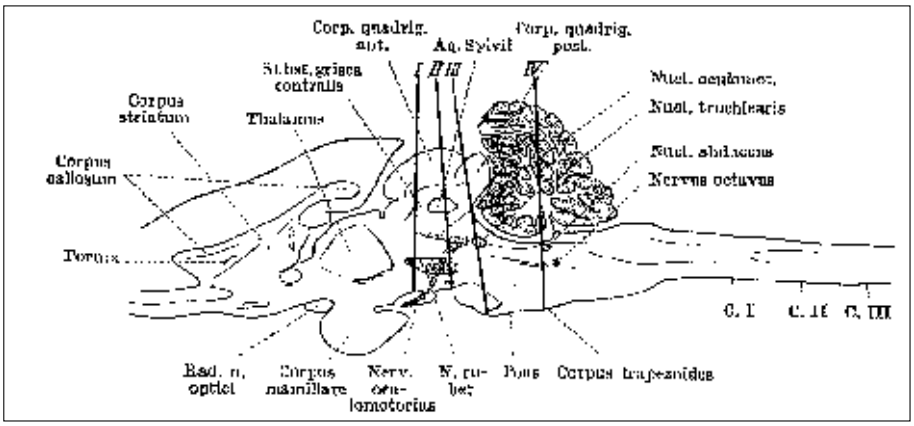

Figure 2. From Magnus: transverse sections in rabbit: different reflexes.

He recommenced studies in dogs, whose thoracic spinal cord had been sectioned. The results did not indicate unequivocally that the intervention produced changes in the central connections, as had been demonstrated in vertebrates. Reflex-sensitivity of the muscles in the hind legs did increase, suggesting some change in sensitivity in the

motor centres of the spinal cord. Magnus recorded these reflexes also on film, parts of which were included in a paper, published in . Subsequent studies showed that the results essentially depended on the intactness of the proprioceptive fibres of the ipsilateral muscles.

He subsequently examined decerebrated animals, in which the brain stem had been severed at different levels between the posterior half of the medulla and the anterior half of the mesencephalon. This resulted in the familiar pattern of decerebrated rigidity, in which all extensors are in a permanent state of maximal contraction, while the flexors are relaxed. Experiments, in particular those of Rademaker, demonstrated that the intactness of the red nucleus is essential for the change from decerebrate rigidity to normal distribution of tone, and that the rubrospinal tract carries the impulses down to the spinal cord.

The study of attitudinal reflexes forced Magnus and De Kleyn to discriminate between the influences of the tonic labyrinthine reflexes and the tonic neck reflexes. Neck reflexes could be excluded by cutting the first three posterior (sensory) roots or by bandaging head, neck and thorax. Labyrinthine reflexes were excluded by extirpation of the labyrinth. It appeared that all attitudinal reflexes could be attributed to the cooperation of labyrinthine and neck-reflexes. The general rule was that every group of muscles reacts to the algebraic sum of stimuli arising from the labyrinth and neck receptors, so that if the extensors of one forelimb acquire increased tone from both the labyrinths and the neck, the limb will be strongly extended, whereas if their tone is increased by the labyrinths and decreased from the neck it may remain unchanged.

Righting reflexes cannot be studied in a decerebrate animal. They can best be studied in a mid-brain animal or thalamus animal, in which the forebrain had been removed so that no voluntary corrections are possible. There are various groups of righting reflexes: labyrinthine, body reflexes acting on the head, body reflexes acting on the body and neck righting reflexes. Higher animals such as cats, dogs and monkeys with intact cerebrum show a fifth group, the optical righting reflexes.

Another clear result from the experiments was that these postural reflexes are undisturbed after extirpation of the cerebellum, and therefore the cerebellum does not play a role in body posture.

In a separate chapter of his book, Magnus discussed extensive pharmacological studies on postural reflexes. Different drugs appeared to have considerably different effects on the various reflexes. The final chapter concerned investigations on postural reflexes in newborn animals.

Personality

Rudolf Magnus and his wife Traudl both came from well-educated, cultured, intellectual, liberal Jewish families. He was of small stature and for that reason got the nickname 'Winzig' (Tiny). He felt at home in Utrecht, but kept intensive contacts with relatives and friends in Germany. According to Otto Magnus ( ), the family was

harmonious. Traudl took care of the upbringing of children, running the household, the finances and the social activities. After dinner, Magnus went to his study to work and did not want to be disturbed. Like his father, Magnus enjoyed hiking in the mountains and holidays were often spent in the Alps. He also liked figure skating. Detailed reports of his journeys, describing both the surroundings as well as the scientific meetings, were mailed home to his parents as well as his own family. He was a gifted speaker and teacher (Oljenick). His list of publications containing over items not only testifies to his abounding energy, but also reveals his knowledge and insight in wide areas of science. As well as being a first-rate pharmacologist and physiologist, he was anatomist, botanist, philosopher and historian.

The awards he received confirm that his impressive contributions were recognised. In , he was elected as member of the Royal Academy of Sciences in the Netherlands. That same year he received, together with De Kleyn, the Guyot prize from the University of Groningen. In the Queen of the Netherlands appointed him 'Knight in the Order of the Dutch Lion'. The Royal College of Physicians in London awarded him the Baily Medal in . One year later, he was invited to present the Cameron Prize lectures in Edinburgh. In , posthumously, he received the 'Hans Horst Meyer Medaille für Fortschritte in der Experimental Medizin' [medal for progress made in experimental medicine] from the Austrian Academy of Sciences.

It was not until that it was revealed that Magnus, together with De Kleyn, had been a serious candidate for the Nobel Prize. In *Nobel, the man and his Prizes* ( ) one can read:

> "The investigations of R. Magnus and A. de Kleyn referred to above concerned tone and posture in different circumstances. It was found that the rigidity developing in decerebrate animals after transsection of the brainstem, especially in their limbs, depends to a large extent on the position of the head. A more detailed analysis revealed that this was a question of tonic reflexes, which were affected partly by the position of the head in space and partly by its position in relation to the neck. Both groups, which can reinforce or weaken each other according to a definite pattern, have been combined under the name of attitudinal or standing reflexes since they enable the animal to stand up. These reflexes can also be observed in normal, intact animals; they play an important part in all habitual movements. While a decerebrate animal can stand up but is not able to get up on its feet, it can get up if the cerebrum alone has been removed, provided the big nerve centres or ganglia situated at the base of the brain are left intact. This ability is due, as Magnus and De Kleyn discovered, to a special group of 'righting reflexes', which are elicited, partly by the vestibular apparatus in the inner ear, and the neck, partly by the eyes, and, partly, by the trunk of the body. It is these complex reflexes, which enable a cat always to land on its feet. Obviously, they are also of the utmost importance in man."

The works of Magnus and De Kleyn were declared by the examiner ( ) to clearly deserve a prize, and the prospects for an award seemed most favourable when Magnus died.

The Rudolf Magnus Institute

Magnus's first laboratory was housed in 'Leeuwenbergh', a church-like building, founded in as a hospice for plague victims. The founder of Dutch chemistry, Gerrit Jan Mulder had used it for his laboratory in the th century. In view of the cramped conditions in Heidelberg, Magnus was happy with this institute. Many of the experiments on body posture and practically all of the photography were done in the open air in the courtyard.

Magnus wrote a letter to the board of trustees in , indicating that the Institute had become entirely inadequate and he requested new equipment. Repeated requests over a number of years remained unsuccessful. When Magnus was offered the chair of the physiologist Hamburger in Groningen, where a new laboratory had been built twelve years before, he seriously considered moving. Magnus was also offered the chair of Pharmacology in his Alma Mater in Heidelberg about . The dean of the faculty immediately brought this to the attention of the trustees and, with the help of the Medical Education Division of the Rockefeller Foundation in New York and the Dutch government, the university decided to found a new pharmacological laboratory. This fact may have played an important role in Magnus's decision to decline the invitation from Heidelberg.

The cornerstone of the new Institute Nieuw Leeuwenberg was laid in . It was opened in the autumn of , but because of his sudden death Magnus never saw the completion of his new institute. His successor, Ulbe Bijlsma (-), inaugurated it in and headed the institute until . In David de Wied (b.) was called from Groningen to take over the chair of Pharmacology. He arranged for the Institute to be named the 'Rudolf Magnus Institute' (RMI) at the occasion of its founding years ago. At a special ceremony, Magnus's grandson Jan R. Magnus unveiled a commemorative stone in the façade of the building. The RMI moved to the new university campus at the outskirts of Utrecht, the 'Uithof' in .

Note

* The author gratefully acknowledges the assistance of Dr. Otto Magnus, who provided him first with a paper on Rudolf Magnus, and later with an entire monograph: Rudolf Magnus: physiologist and pharmacologist ( ). The current biography is based primarily on this material.

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