THE DEPARTMENT OF ANATOMY - FROM 1961

By Gunnar Grant

Foto: Lennart Nilsson

with contributions from

Staffan Cullheim

Brun Ulfhake

Mårten Risling

Jan Ekholm

To give an insight into the research environment at the former department of anatomy and the research groups emanating from this department it is essential to give a background of what has happened over the years since the 1960ies. This is the more important, since the existence of the department was based originally on its role in the teaching of medical students, and not on research, and the teaching responsibility has to a large extent influenced the size of the department and its staff.

In the history of Karolinska Institutet 1910-1960 Ture Petrén wrote about the anatomy in Stockholm during those years. Dramatic changes have taken place since then. The most drastic change was that the subject of anatomy represented as a separate department disappeared, in connection with the so-called KI93 reform. The former department, the oldest preclinical department at KI, was fused with the department of histology and cell biology and with the department /Nobel Institute/ of neurophysiology, creating a new department of neuroscience. At the same time parts of the former department of histology separated and became part of a newly created department of cell and molecular biology, CMB. Since the 1960ies the research at the anatomy department had been focused mainly on the nervous system and therefore, approaching the fusion of departments which had been proposed in KI93, a fusion seemed rather natural. Before 1993 KI had 153 departments. After the fusions

they were reduced to 35[1]. Historically one can go back to 1945, a few years before the move from Kungsholmen to Solna. By that time KI had 30 departments.

Other main changes have been related to the increased number of students.
In the 1960ies the anatomical teaching included medical and dental students. The number of medical students was 208 per year (104 per term). In the early 1970ies there was an increase up to 370 (185 per term). With this increased number the lecture hall and the unit for anatomical dissection in the anatomy-histology building became too small. Sune Bergström, then rector at KI, managed to get a separate building for the undergraduate teaching at KI, the Berzelius lab, erected. It was finished in 1971. The lecture hall could take 300 students and the teacher who gave a lecture could at some lectures, which were given simultaneously to medical and dental students, face no less than 295 students. In 1992 there were still around 170 medical students per term, but the number of dental students had decreased to around 60. On the other hand around 70 physiotherapy students had been added. The staff of teachers had to be adapted to the situation, as commented on below.

Not only the teaching activities moved from the different preclinical departments. Also the whole department of histology got new space in the Berzelius lab. This, in turn, meant that the anatomy department was given the opportunity to expand into all of the former histology department localities.

The chairman of the anatomy department was now Sten Skoglund.


Sten Skoglund

He had been appointed in 1968 at the retirement of Ture Petrén.


Ture Petrén

Skoglund had a very active group of graduate students, all working on the nervous system, some of them using electron microscopy.

Footnote 1: Figures from "Från läkarskola till medicinskt universitet: Karolinska Institutets ledning 1953-2012." by Inger Huldt, Daniel Normark, Bengt Norrving.

Scientifically active was also Sven Carlsöö, whose interest was kinesiology. He held a position as Reader (prosektor-biträdande professor [2]) shared between medicine and dentistry, created in 1962. But he was about to retire in 1972.

Sven Carlsöö

His follower became Lars-Gösta Elfvin, an electron microscopist focusing on the autonomic nervous system, trained by Fritiof Sjöstrand, one of the pioneers in electron microscopy.

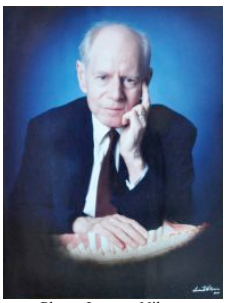

Photo: Lennart Nilsson

Lars-Gösta Elfvin

The department also had a position as Reader tied to medicine, created in 1911. This position had been held by Skoglund for five years before he had got his professorship. This chair had now been filled by Gunnar Grant, a neuroanatomist appointed in 1970.

Photo: Lennart Nilsson

Gunnar Grant

He came from Uppsala and was trained in neuroanatomy by Bror Rexed and also by Alf Brodal at the Oslo school of neuroanatomy. By the time when Grant got his position an appointment was also combined with money for equipment. Skoglund had already had that possibility and had his laboratories well equipped. The money available when Grant got his position covered almost all of what he wanted, so he got a very good start. Moreover, he had brought three of his collaborators from his previous laboratory in Uppsala with him.

Footnote 2: The position as ”prosektor” was changed to ”biträdande professor” in 1969

The year after Grant had arrived, in the summer of 1971, a dramatic change occurred. Skoglund died quite unexpectedly by a heart infarction, at the age of 42. Carlsöö, who was about to retire, offered to take care of coming evaluations for positions, but Grant had to take over the chairmanship. With the support of senior staff members supervisors were found for most of Skoglund´s graduate students and the normal duties of the department, the teaching of medical and dental students, were taken care of.

Time had also to be spent with the architects for pursuing the planning started by Skoglund for the part of the building left by the department of histology. Here a new high class animal facility was placed in the basement, being moved from the top floor of the anatomy section of the building, and laboratories and offices were planned in the two floors above. These were greatly needed. Temporarily, space for laboratories had been arranged in the so-called Lab 67, close to the department of physiology, to cover the need for Grant´s research group. Both Grant and Elfvin got laboratory and office space in the renovated part of the building left by the histology department. The space left by the former animal facility was renovated and the division for education, with its head Eyvor Wahlbom, moved in.

An important change for the anatomy departments by this time was the introduction of a new system with donations by free will for receiving bodies for dissection. Bror Rexed, who had been professor of anatomy in Uppsala was behind this and the system was received very positively and is still working very well. Until this time patients who had died at a mental hospital and had no relatives should be handed over to an anatomical department for dissection, a rule existing following the abolition of death penalty in Sweden in 1921. Skoglund had implemented the new system in Stockholm and soon there were a large number of donations. This also meant that the students now had access to dissections after a long period when lack of human bodies for dissection had been a great problem.

The teaching, including the dissection of human bodies was an important part of the activity for the department. Skoglund had designed the new dissection unit in the Berzelius lab with the idea to give instructions to the students from a special TV studio. TV was a new tool in this situation, but Grant had been involved in testing TV for anatomical teaching as a member of a project group for television and radio in education, the so-called TRU-committee, appointed by the Minister of Education and Ecclesiastical Affairs, Ragnar Edenman. He had also participated in a course in TV production and produced a colour-TV program about the surface anatomy of the neck. He initiated a TV course with a producer from the Swedish television, Claes Wirsén, former assistant professor in histology at KI, a technical expert from KI, and a group of anatomical teachers. Following this course the internal TV installation became used for general information, teaching related information and instructions for group work.

A re-organization of the curriculum took place in 1974, following the so-called Werkö investigation, dealing with the first three years of the medical studies. At KI this resulted in a reduction of the anatomy course from 23 to 18 weeks. Two of these were placed during the first term and were devoted to studies of basic facts in systematic anatomy. The remaining 16 weeks were placed during the second term and devoted to regional anatomy, with a focus on topographic and applied anatomy. Organ embryology with certain clinically relevant malformations was dealt with directly after the adult anatomy of the region in question had been dealt with. The details of the new course were worked out by joint efforts by the teaching staff at the department. It was later, in 1977, described in Läkartidningen with the

aim to be known also by the clinically active colleagues. This new course meant an orientation towards even more clinically relevant elements than before, e.g. with the introduction of clinical laboratory elements and with selected clinicians invited to give clinical aspects that could supplement what the anatomy teacher had presented. The general outline of this course was kept also after the introduction of the KI93 reform, although it was then shortened to 12 weeks, partly due to an integration of the earlier course on the anatomy of the nervous system into the neuroscience course.

With the great teaching responsibility for the department and due to the increase in the number of students, including both medical, dental and physiotherapy students, as commented on above, the department also had a big teaching staff. In 1992 there were 40 teachers altogether. Twentyone of them were licenced doctors, 4 were dentists and 11 had defended their doctoral theses.

A research education reform from 1969 had meant, i.a., that the positions as professor, associate professor (docent) and assistant professor (forskarassistent) were reserved mainly for teaching and instruction–supervision in the research education. This did not mean, however, that they should not be involved in the teaching of the undergraduate students. Actually, Petrén had been very much involved in the teaching of the medical students. In addition, he had devoted much of his time writing textbooks in anatomy. These were highly praised, and they are still very useful. The research at the department during his later years had been very actively represented by Fritiof Sjöstrand. He had guided many students, who had graduated. In 1958 he left, however, for a position at UCLA in Los Angeles. His remaining students, Isser Brody, Lars-Gösta Elfvin, Sven-Erik Nilsson and Arvid Maunsbach all later graduated in Stockholm, however, after having been over to the US for shorter or longer times. Elfvin graduated in 1963 and his thesis was on the nervous system: ”Electron microscopic studies on the splenic nerve, the superior cervical ganglion, and the sympathetic trunk of the cat.” Among former students of Sjöstrand, both Johannes Rhodin and Maunsbach were later appointed professors at the department, filling the chair after Skoglund, one after the other, Rhodin formally from 1976 to 1980 and Maunsbach from 1983 to 1984. In practice, however, Rhodin held the professorship actively just for 2 years and 5 months, and Maunsbach just for 3 months.[3]

With Skoglund, the scientific profile of the department became neuroscience. Carlsöö, who had been trained as a dentist, had focused on kinesiology and had been supervisor for, probably, four of the dentists graduating from the department in the early 60ies.[4] His line of research was taken over by **Jan Ekholm – see below.**

When **Sten Skoglund** had got his position as Reader (prosektor) in 1963 he had a very active group of young graduate students, who had joined him from his laboratory in Uppsala, all working on the nervous sytem. In addition he recruited Jan-Olof Kellerth as associate professor (docent) from Ragnar Granit´s Nobel Institute for Neurophysiology. That was the

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Footnote 3: The position was later advertised as professorship in biological structural research and filled by Sven-Olof Bohman, a former student of Maunsbach, He held it from 1988 to 1991,when he died from a malignant disease. The chair was later re-named professorship in molecular structural biology and placed at an other department.

Footnote 4: Gösta Lindholm, Birgit Thilander, Ulf Rutberg, Erik Rönnholm

place where Skoglund also had started his scientific career, but in 1954 he had joined Bror Rexed to Uppsala, where Rexed had got the professorship in anatomy. Skoglund had soon his students graduating, the first one´s in 1967. His own thesis, which he had defended in Uppsala in 1956, dealt with the knee joint innervation in the cat. Now, in Stockholm, all of his students focused on the postnatal development of the nervous system, studied mainly in the cat, which by this time was the preferred experimental animal. The first student under Skoglund to present his thesis was Jan Ekholm. The title of his thesis was ”Postnatal changes in cutaneous reflexes and in the discharge pattern of cutaneous and articular sense organs. A morphological and physiological study in the cat.” His next student was Gösta Schwieler, whose thesis had the title ”Respiratory regulation during postnatal development in cats and rabbits and some of its morphological substrate”. This was also presented in 1967. The following year Bo Nyström and Claes-Henric Berthold defended their theses. Nyström´s thesis had the title ”Postnatal structural and functional development in the efferent neuromuscular system of the cat” and Berthold´s ”Ultrastructural and light microscopical features of postnatally developing and mature feline peripheral, myelinated nerve fibres”. With Berthold´s thesis Skoglund had incorporated electron microscopy in the methodological arsenal, and Berthold´s thesis was an important contribution. Electron microscopy was also used in the thesis by Sebastian Conradi, in 1969, and in the one by Claes Hildebrand, in 1971. Conradi´s thesis, ”On motoneuron synaptology in cats and kittens” became an important contribution to the field and a frequently quoted paper. The same was true for Hildebrand´s ”Ultrastructural and light microscopic studies of myelinated nerve fibers in the adult and developing feline central nervous system”. Mention should also be made of Anders Mellström, whose thesis ”Postnatal motoneurone size and excitatory changes in the cat” was presented the same year as the one by Conradi.
Skoglund had some more students, some of whom got new supervisors in the department in connection with his unexpected death. Just a few quitted.
Skoglund had also given space in one of the laboratories for Eric Fluur, neuro-otologist, who guided Jan Siegborn in his work on ”Interaction between the otolith organs and the semicircular canals”, resulting in his dissertation in 1975.

Sebastian Conradi took on Lars-Olof Ronnevi as PhD student, and Ronnevi presented his thesis ”On spontaneous postnatal elimination of boutons from cat spinal motoneurons. An electron microscopic study” in 1976.
This thesis gave evidence for a normally occurring postnatal elimination of synaptic terminals from the cell body and axon hillock of spinal motoneurons. This elimination could be executed by neighbouring glia or the motoneurons themselves by engulfment end disintegration, and could lead to a reduction of synaptic terminals on the cell soma by about 50%.

As mentioned above, **Jan-Olof Kellerth** was recruited to the department of anatomy by Sten Skoglund after completion of his thesis (”Postsynaptic inhibitions in cat spinal motoneurones stimulated by muscle stretch. Effects of strychnine and picrotoxin”) in 1966 with professor Ragnar Granit at the Nobel Institute for Neurophysiology as supervisor, the year before Granit was awarded the Nobel prize in physiology or medicine. Kellerth was in fact Granit’s last PhD student. Through this recruitment, the department got access to intracellular recording techniques in live animals, which proved very valuable to combine with anatomical and histological methodologies. Kellerth’s first PhD student was Cary Hammarberg (”On the postnatal differentiation of motor units in the cat ankle muscles. A histochemical and

physiological study.") 1975. This thesis represented a continuation of Skoglund's interest in the development of the nervous system.

Albeit much warranted there was no technique available at this time to study both electrophysiological and morphological properties of single neurons in the brain and spinal cord. Early attempts to inject fluorescent dyes, such as Procion Yellow, into the cell body of identified neurons was of limited value, since these substances were often toxic and remained in the cell soma and entered dendrites and axons to a very limited extent. A major breakthrough in the attempts to visualize neurons that had been studied electrophysiologically came through the use of horseradish peroxidase (HRP). This substance had been used to demonstrate the retrograde transport of protein in axons with Krister Kristensson and Yngve Olsson as forefront researchers in the field. Since Kellerth had experience from Procion Yellow injections in spinal motoneurons, it was a natural development to try to inject HRP into cell bodies of identified motoneurons through glass microelectrodes. These attempts were done together with Kellerth's second PhD student, Staffan Cullheim.

In 1976, three papers were published, which all made use of intracellular injections of HRP in single spinal cord neurons and axons. All three studies were in fact made in European laboratories (Alan Brown's in Edinburgh, Elzbieta Jankowska's in Gothenburg and Jan-Olof Kellerth's at KI). Two properties of the HRP were essential to rank this methodology as a breakthrough. First, the HRP was transported into the dendrites and axons, including axon collaterals of the studied neuron, providing a hitherto unknown complexity of the dendritic trees and axon arborizations. Second, the method för visualization of HRP provided a reaction product which was electron dense, i.e. it could be studied at the ultrastructural level. In this way, the paper by Cullheim and Kellerth in 1976 could present the first true picture of the enormous dendritic tree of a spinal motoneuron, as well as the first ultrastructural visualization of a synaptic terminal of a motor axon collateral in the spinal cord.

With this new methodology, a number of PhD students were recruited for thorough studies of spinal motoneurons, and the following theses were produced:

Staffan Cullheim ("On axons and axon collaterals of α-motoneurones in the spinal cord of the cat. A morphological study using intracellular deposition of horseradish peroxidase.") 1978. In this thesis was described the method for intracellular HRP staining of single motoneurons in the spinal cord, as mentioned above. The main focus was the description of the motor axon collaterals in the cord, which were postulated to contact Renshaw cells, which in turn inhibit motoneurons with the same function as the parent cell (recurrent inhibition). It was found that fast-twitch motoneurons had much larger axon collateral trees than slow-twitch motoneurons, while short plantar motoneurons lacked axon collaterals completely. A novel finding was that motoneurons through their axon collaterals make direct synaptic contacts with other motoneurons suggesting a firing output interaction between motoneurons hitherto not known to exist.

Per-Åke Lagerbäck ("On α-motoneuron axon collateral boutons and Renshaw cells. An electron microscopic study in the cat.") 1982.
This thesis provided detailed information on the ultrastuctural characteristics of motor axon collateral synapses, presumably containing acetylcholine as transmitter substance, on Renshaw cells and other motoneurons. Also Renshaw cells were injected with HRP, which allowed for a detailed light and electron microscopic description of the cell body, dendrites and axon arborizations of these cells.

Brun Ulfhake (”The dendritic trees of motoneurones in the lumbosacral spinal cord of the cat. A morphological and physiological study.”) 1982.
In this thesis, intracellular recordings of passive and active membrane properties of spinal α-motoneurons were combined with intracellular labeling with HRP (see above) and twitch and fatigue properties of the motor units enabling classification into motor unit type (see above). The most significant finding was that across dendritic branching points the postulated *3/2-power rule* of Rall was obeyed implying that current density would be conserved and that the size (in terms of membrane area and branching complexity) of a distal dendritic arborization could be inferred from the caliber of the stem. Another important result was that low-threshold motoneurons were smaller (soma and dendritic trees) than high-threshold motoneurons, bringing together the *size-principle* of Henneman with the doctrine that *motor units are recruited according to motor unit type*.

Lars Gollvik (”The effects of tenotomy and overload on the postnatal development of motor units in the cat”) 1988.
In this thesis intracellular recordings and HRP labeling of α-motoneurons were correlated with motor unit twitch and fatigue properties and muscle fiber type using enzyme histochemistry in skeletal muscles subjected to chronic unload and overload. Early chronic tenotomy was used to unload skeletal muscles and in parallel overload synergists during the postnatal period when the adult characteristics of motor units develop as shown in C. Hammarberg’s thesis (see above). Unloading impacted motor unit differentiation, the postnatal remodeling of the motoneuron’s dendritic tress, and caused degeneration and loss muscle fibers. Combined these results evidence that muscle tension is non-redundant for the development of adult motor unit characteristics. Overload had marginal impact except for the anticipated muscle hypertrophy response.

In 1980 Kellerth got a professorship in anatomy in Umeå and moved the laboratory there. Following a postdoc period at NIH 1982-83, Cullheim returned to the department and could with support from Grant and Elfvin and together with Ulfhake rebuild a laboratory for intracellular studies to the same standards as during the time with Kellerth.

Staffan Cullheim and **Brun Ulfhake** collaborated extensively, and there were also strong interactions between Cullheim, **Claes Hildebrand** and Hildebrand’s PhD student Mårten Risling**.** Thus, Cullheim and Ulfhake published a series of extensive studies on the postnatal development of dendritic trees and axon collaterals of spinal motoneurons, as well as studies of adult gamma motoneurons, using the intracellular HRP technique. The studies with Risling and Hildebrand, again using the intracellular HRP labeling technique, gave the unexpected finding that spinal alpha motoneurons had the capacity to regenerate new axons after a cut lesion within the spinal cord, sometimes even with a dendritic origin (”dendraxons”), thus challenging the concept that regeneration of axons in the central nervous system was not possible. These studies led with time to experiments where ventral roots that had been torn from the spinal cord surface were reimplanted into the cord. Such reimplantation could be shown to successfully lead way for new axons from lesioned motoneurons to reinnervate denervated muscle. Eventually, these findings have led to the introduction of a surgical technique in human cases of root avulsion by the hand surgeon Thomas Carlstedt, who was recruited to a position in England, based on these achievements.

The interest in motoneuron connectivity raised in the Cullheim-Ulfhake lab led to a strong interaction with Tomas Hökfelt at the department of histology. Hökfelt had made the seminal

discovery of neuropeptides as neurotransmitters, colocalized with 'classic' transmitter substances. The first PhD student in the Cullheim-Ulfhake lab, Ulf Arvidsson, performed a number of extensive studies on the descending 5-HT system and coexisting peptides.

Ulf Arvidsson ("On the 5-HT bulbospinal system in cat and monkey. Studies of distribution and coexisting compounds with special reference to the lumbar motor nuclei") 1991.
It was found that the spinal motor nuclei in cat and monkey receive a dense innervation of 5-HT fibers. These fibers harbor also to a large degree the peptides SP, TRH and GAL in cat and SP, TRH and CGRP in monkey. In both species, 5-HT terminals make synaptic as well as non-synaptic contacts with motoneurons. The cells of origin for the 5-HT fibers containing peptides are in both species located supraspinally in the raphe nuclei and nucleus reticularis lateralis.

In the late 80ies and early 90ies Cullheim and Ulfhake started to follow own courses, with a strong interest in motoneuron lesion models by Cullheim, and an aim towards studies of aging of motor units by Ulfhake. They kept a common line of interest in the identy of transmitter substances in synapses onto the motoneuron, however, leading to a fruitful collaboration with Ole Petter Ottersen in Oslo, who had managed to visualize the presence of amino acids in nerve endings at the ultrastructural level. The thesis by Örnung will be presented under heading **Brun Ulfhake.**

Staffan Cullheim´s main research profile from the end of the 80ies has been the response of spinal motoneurons after axon lesion. Thus, this was the subject for a number of PhD projects listed below. Cullheim became Reader (biträdande professor) in 1997 and full professor in anatomy in 1999. During the years 2000-2003 he was deputy chair of the department of neuroscience and chaired the department 2004-2011.

PhD students:

Ulf Arvidsson 1991 (see above)

Hans Lindå ("Studies on spinal motoneurons after intramedullary axotomy") 1992.
After a cut lesion of motor axons in the ventral funiculus of the lumbar spinal cord, about half of the population of motneurons survive and display a vigorous regenerative response, as revealed by the outgrowth of axonlike processes through the scar tissue in the cord. The scar tissue has an unusually long-standing defect in the blood-brain barrier and the low affinity neurotrophin receptor is expressed in non-pericytic perivscular cells in the lesion area, which may promote regeneration.

Fredrik Piehl ("Regulation of CGRP expression in rat spinal motoneurons") 1996.
The neuropeptide CGRP is found in most lumbar motoneurons and the CGRP mRNA is upregulated in the motoneurons after sciatic nerve transection. Transection of the spinal cord leads to a decreased expression of CGRP below the lesion. bFGF seems important in the regulation of CGRP levels, in that it downregulates CGRP mRNA in embryonic motoneuron cultures and attenuates the axotomy-induced increase in CGRP mRNA. Thus, the expression of CGRP in motoneurons is regulated in part by target-derived factors, and one physiological role for CGRP may be to control axonal sprouting during development and regeneration.

Henrik Hammarberg ("Spinal motoneurons and molecules related to neurotrophic function after axon injury") 2000.

An upregulation of insulin–like growth factor binding protein (IGFBP)-6 after motoneuron axotomy seems to be counteracted by high levels of IGF-2 in denervated nerve, suggesting roles for successful regeneration. Receptors for the trophic factor GDNF seems prioritized in the regenrative response. Regeneration is also associated with high levels of integrin α7/β1 in the motoneurons, suggesting an important role for laminins in the regenerative events. Moreover, there is a strong upregulation of MHC class I and β2-microglobulin mRNAs in motoneurons after axon lesion, which implies a role for these immunological molecules in the regenerative response.

Johan Hellström (”On the cholinergic C-bouton”) 2004.
The large and very specialized C nerve terminal/synaptic bouton with acetylcholine as transmitter expresses proteins necessary for fast, Ca^{2+}-sensitive neurotransmission. The number of C boutons is smaller on motoneurons innervating distal foot muscles, whereas ocular motoneurons lack such boutons completely. A postsynaptic target for C boutons is the muscarinic m-2 receptor, as revealed by immunohistochemistry. The source of the spinal C boutons is found in the spinal cord itself.

Wilhelm Wallquist (”On laminins and laminin receptors and their roles in regeneration and myelination of the peripheral nerve”) 2004.
mRNA levels for the laminin receptor integrin subunits α6, α7 and β1 are profoundly upregulated in adult spinal motoneurons after sciatic nerve transection, and immunoreactivity of these subunits is found in regenerating axons in peripheral nerves. After nerve transection, laminin α2, α4, β1 and γ1 chain mRNAs and immunoreactivities are upregulated in close relation to axons in the nerve. This indicates that laminin-2 (α2β1γ1) and laminin-8 (α4β1γ1) are important for the regeneration. Absence of the α4-chain, which unables laminin-8 to form, leads to a disturbance in radial sorting and impaired myelination of peripheral nerves.

Stefan Plantman (”Cell-matrix interactions in neuronal regeneration: Focus on integrins and laminins”) 2008.
Upregulation of integrin mRNAs in neurons is closely correlated with regenerative ability. Absence of laminin a4 results in a pronounced dysmyelinating neuropathy. Laminin-1 and -10 are superior to laminin-2 and -8 in supporting neurite growth from adult DRG neurons. Adult DRG neurons use integrins α7β1 and α3β1 to grow on laminin-1 and -2, and α6β1 to grow on laminin-8 and -10. Neuronal myosin-X is upregulated after peripheral nerve injury and mediates growth of neurites on laminin.

Johan Zelano (”Adhesion molecules and synapse remodeling during motoneuron regeneration”) 2009.
Lesioned motoneurons increase their expression of cell-cell adhesion molecules nectin-1 and -3 and necl-5 with a localization of the proteins suggesting involvement in neuron-glia interactions both in the spinal cord and the peripheral nerve. Axotomized spinal motoneurons decrease their expression of SynCAM1 and NLG2 and -3 during the phase of synaptic removal from lesioned motoneurons with a resoration during the return of synapses. This indicates a role for these molecules in the maintenance of synaptic inputs onto motoneurons.

Sebastian Thams (”Immune recognition molecules in synaptic plasticity and regeneration of spinal motoneurons”) 2009.
Immunoreactivity for the immunological protein MHC class I is found in motoneuron somata, but also, and predominantly, in axons and presynaptically at neuromuscular junctions (NMJs). Peripheral nerve lesion induces a strong increase of motoneuron MHC class Ia mRNA,

indicating a role for MHC class Ia molecules during regeneration. Accordingly, there was an accumulation of MHC class Ia proteins at the cut ends and in growth cones of motor axons after lesion. Muscles from mice lacking MHC class Ia display an increased density and a disturbed distribution of NMJs compared to wild-type mice. Mice lacking functional MHC class I also displayed a deranged pattern of the removal of synapses from the cell soma of motoneruons following axotomy, indicating a role for MHC class I also in the spinal cord.

Alexander Berg (”Elimination of synapses from injured motoneurons – a model for study of synaptic plasticity in the adult central nervous system”) 2013.
Complement proteins C1q and C3 are both up-regulated in the neuropil surrounding motoneruons following sciatic nerve transection. Complement C3 deficient mice exhibit a hampered stripping of synapses from the cell body of lesioned motoneurons, leaving most of putative inhibitory inputs intact. However, absence of the upstream complement protein C1q does not affect this phenomenon. Thus, the effect seems to be mediated via a non-classical complement pathway. C3 deficient mice also display an increased GAP-43 expression in regenerating motoneurons, mirroring a stronger regenerative response. This is confirmed by a faster functional recovery in C3 deficient mice compared to wild-type mice.

Brun Ulfhake’s main line of research from the early ’90 and onwards was to explore alterations in neuronal signaling, motor unit function and sensory mechanisms during aging. Later-on more general aspects of mammalian aging were addressed including alterations in metabolism, the microbiome and the beneficiary effects of caloric/dietary restriction. This work was carried out by research students (see below) and visiting postdocs. After returning from a postdoc in R. E. Burke’s lab at NIH, Bethesda (see above), Ulfhake became lecturer of Anatomy in 1994 and professor of Anatomy in 2001. In 2012 he was recruited by the President (of Karolinska Institutet) to help build Comparative medicine together with Björn Vennström and Ulfhake served as Chair of Comparative medicine 2013-2018.

Thesis students:

Vania Ramírez-Léon (”Morphological and immunohistochemical studies on the organization of sacral motoneurons”) 1997.
The thesis elucidated developmental and aging-related changes in the dendritic trees of somatic sacral motoneurons and the peptidergic-, serotoninergic- and amino acid transmitter input to these motoneurons. The studies showed that dendritic tree remodeling including neosynaptogenises is extensive during the early postnatal period but occurs also late in life. The spatial distribution of transmitter-identified projections onto these motoneurons was found to be non-random and motoneuron dendrites in the Onuf’s nucleus innervating the pelvic floor and midline skeletal muscles receive synaptic input via boutons also synapsing with adjacent dendrites. Such dendrites were in turn interconnected via puncta adherentia/desmosomes. Combined this interconnectivity of presynaptic and postsynaptic profiles was proposed to facilitate synchronization of motoneuron output needed for continence as well as emptying of bladder and bowel, and ejaculation.
Late in life axonal aberrations with demyelination, atrophy and axonal dystrophy become prominent features of the neuropil and this thesis provides the first ultrastructural description of the early phase of axonal dystrophy when the enlarged distal axon ending is still in synaptic contact with the target. Dystrophic axons were often enriched with glutamate over the synaptic vesicles and contained increased levels of glutathione peroxidase suggesting that glutamatergic pathways are vulnerable to develop dystrophy and that redox stress is a component of this degenerative aging-related process.

Göran Örnung (”On amino acid neurotransmitters in the spinal cord motor nuclei”) 1997.
In this thesis representing a joint collaborative effort with Cullheim’s and Ottersen’s research groups (see above), colloidal gold post-embedding immunohistochemistry and electron microscopy was used to map established and putative amino acid transmitters in synaptic boutons of the spinal cord. While homocysteine, aspartate and taurine were not found to accumulate over bouton endings or synaptic vesicles, glutamate, glycine and GABA were enriched over the synaptic vesicles suggesting that the three latter but not the former three amino acids serve as classic transmitters in the feline spinal cord. Corroborating the electrophysiological evidence of Cullheim and Kellert (see above) that recurrent inhibition of α-motoneurons is mediated by both glycine and GABA, this thesis demonstrate the frequent co-localization of glycine and GABA in the same synaptic bouton (~25% of all boutons) suggesting the co-release of these classic neurotransmitters. Systematic mapping of glutamate, glycine and/or GABA across the soma-dendritic domains of spinal motoneurons revealed that ~94% of all synaptic boutons contained glycine and/or GABA, or glutamate. There was a clear bias towards boutons with glycine or glycine co-localized with GABA on the soma and most proximal dendrites, while only 5 % contained GABA only and <20% contained glutamate. Onto more distal dendritic domains the frequency of glutamate boutons increased to 38%.

Birger Ragnarson (”The Central Cervical Nucleus in the rat”) 1998 (together with Gunnar Grant, see separate heading).
This thesis was conducted in collaboration between Grant’s, Ottersen’s, and Ulfhake’s research groups and included studies on the connectivity between cerebellum and the CCN (*for details see under the heading of Grant*) and studies mapping transmitter-identified input to cervical motoneurons and neurons of the CCN in small rodents (in Ulfhake’s lab). Based on a method developed by Ragnarson and Örnung, an actively transported tracer substance (CTB) could be made visible on the ultrastructural level by colloidal gold technique. By combining tracer labeling with immunogold visualization of amino acid transmitters and cognate receptors they show for example that CTB labeled Ia afferent boutons synapsing with CTB labeled α-motoneurons are enriched with glutamate over the synaptic vesicles and that the opposing postsynaptic membrane target α-motoneurons contained the complementary glutamate receptors (GluR 1-4).

Hans Johnson (”Spinal Motoneurons and the Bulbospinal Serotoninergic System in Aged Rats with Behavioral Deficits”) 1998.
In this thesis behavioral assessments were introduced to describe the aged phenotype of small rodents at different chronological ages across life-span. Using immunohistochemistry, in situ hybridization, chemical analyses and lesions, it could be shown that the density of motoneurons was not very different between adult and aged rats (~-10% at the median survival age of the rat strain used) while a number of the aged motoneurons expressed increased levels of mRNA and protein of calcitonin-gene related peptide and growth-associated protein 43; as well as lowered levels of trk (B and C) receptors (responsible for the signal transduction of target derived neurotrophic factors (NT3, BDNF and NT4). An expression profile very similar to the aged motoneuron phenotype could be induced in young adult rat motoneurons by experimental axon lesioning. Thus, the data suggested that aging-related muscle atrophy (sarcopenia) may be driven by a failure of the aged motoneuron to sustain axon contact with all its target muscle fibers in the motor unit and that a decline in motor capacity may occur long before motoneurons are lost. Further, a correlation between

the extent of motor impairment and the number of motoneurons disclosing an aged phenotype was established on the level of the individual.
The serotoninergic (5HT) bulbospinal system constitutes an important input to all motor nuclei throughout the spinal cord. In this thesis it is shown that this system is severely affected by aging with a loss of input the motor nuclei being marked at lumbosacral levels but less evident in cervical regions. Based on morphological criteria the dying back of the 5HT bulbospinal pathway is likely due to axonal dystrophy. A correlation was established between the extent of loss of 5HT input to the lumbar motor nuclei and the severity of behavioral motor impairments of the studied individuals.

Esbjörn Bergman (”Changes in Sensory Systems during Aging: An experimental study in the rat”) 1999.
Behavioral responses to nociceptive and tactile stimuli were used to phenotype aged outbred rats and to correlate these changes to morphological and chemical alterations in sensory systems of the aged rat. Using stereology evidence were presented that loss of primary sensory neurons in male and female rats at cervical and lumbar levels is small (~12%) despite overt deficits in peripheral skin innervation and, further, the loss of neurons did not correlate with behavioral deficits in the individuals. In both target tissues and neurons of the dorsal root and trigeminal ganglia, myelinated large caliber sensory neurons innervating Merkel endings and muscle spindles are more severely affected than medium or small caliber/unmyelinated sensory neurons. Using selective markers for large and small caliber primary sensory neurons further evidence was provided corroborating that aging-related sensory impairments are due to distal processes of the sensory neurons, impacting both the innervation of the peripheral target and the central spinal cord projection of the same sensory neuron. Examination of sensory and mixed peripheral nerves of the lower and upper extremities showed loss of axons, disturbed myelination, axonal atrophy and dystrophy.
Further experiments provided data on reduced levels of trk A/B/C proteins and mRNAs in aged primary sensory neurons and corresponding changes of target derived neurotrophic factors (NGF, BDNF, NT3 and NT4) in the skin. It is concluded that aging of the cutaneous innervation, manifested in degenerative and regenerative events, is strongly associated with changes in neurotrophic interactions between sensory neurons and target tissues.

Susanna Kullberg (”On Age Related Changes in Axons and Glia of the Central Nervous System”) 2002.
In this thesis on aging of outbred rats evidence were provided that in parallel to the emergence of axonal dystrophy and atrophy in the spinal cord, spinal motoneurons loose a significant portion (30-50%) of their synaptic boutons. The loss of synaptic boutons associated with an astrogliosis, the emergence of activated microglia and an upregulation of MHC class I. and β2-microglobulin. A further sign of aging-related axon aberrations was the observation made here of a diffuse de-myelination of the spinal cord white matter and an accumulation of myelin breakdown products along with activation of microglia cells. An important result from these studies was that aging impacts motoneurons and axons of the spinal cord to a variable extent within, and between, animals providing a basis for the claim of successful and less successful trajectories of aging among individuals of the same chronological age. Such differences were also shown to covariate with assessment of sensorimotor disturbances on the level of the individual.

Yu Ming (”Regulation of Neurotrophic Signaling Molecules in Motor Neurons, Primary Sensory Neurons and Target Tissues in Senescence”) 2003.

In small rodents neither motoneurons nor primary sensory neurons are lost to any significant degree even at advanced age but do show characteristic changes in gene expression pattern, cell anatomy and connectivity conferring a distinct aged neuron phenotype. Results from preceding thesis have indicated alterations in signaling of the classic target-derived neurotrophins (NT) with a decreased expression of their cognate receptors in both aged motoneurons and aged primary sensory neurons. Results made here show that the NTs are downregulated in the target tissues and that the degree of change correlate with sensorimotor impairments. In contrast to the classic NTs, glial cell-line derived neurotrophic factor (GDNF) increase in both the target muscles and the peripheral nerves, a change that is accompanied by an upregulation of the GDNF receptors GFRα1 and c-RET in both motor- and sensory neurons. The studies were expanded to include also the family of fibroblast growth factors (FGF), and some of the neuroregulatory and pro-inflammatory cytokines. The results provide evidence for an increased FGF/FGF receptor 1 signaling in both motoneurons and the target muscles. CNTF was also increased in the target muscle along with its receptor gp130. In motoneurons and glial cells of the spinal cord of aged rats, there is an increased expression of interferon-γ and its receptor -a change suggested to be a response to increased break down of myelin and removal of degenerating axons and axon endings. The results also show that TGF-β, IL-β1 and IL6 increase in astroglial cells and it is proposed that these changes may play a role in the astrogliosis present in the aged spinal cord.

Erik Edström (”Sarcopenia”) 2005.
Behavioral tests and measurement of muscle mass across life span showed that outbred rats develop sarcopenia in early aging and at the endpoint (median survival age of this strain) hind limb muscle mass was reduced to one third of life-span peak value. Further, the loss of muscle mass correlated with the behavioral motor impairments on the level of the individual. Analysis of the anabolic-driving signaling machinery in skeletal muscles (IGF-1, IGF/INS tyrosine-kinase receptors, PKB/TORC) and members of the family of myogenic differentiation factors (MDFs; MyoD1, Myog, Myf6) did not support the concurrent notion that sarcopenia is driven by failure of the regenerative machinery intrinsic to the muscles. On the contrary, evidence was presented that at study endpoint key enzymes for myosin breakdown (Atrogin, MuRF1) are downregulated and that this may be due to translocation of Foxo transcription factor from the nucleus to the cytosol through phosphorylation. Based on analysis of protein abundance and protein phosphorylation pattern it was proposed that Foxo phosphorylation is instigated by TORC1 activation through IGF-1/Insulin-TKR-PKB possibly augmented by increased of Shc adapter protein levels evident in aged rats skeletal muscles. An important finding by Edström was that aged sarcopenic muscles re-express two embryonal proteins (CHNR-γ and embryonic MyHC), both indicative of muscle fiber denervation. These findings lend further support to the neurogenic theory of sarcopenia and corroborated Johnson’s characterization of the aged motoneuron phenotype (see above).
Finally, Edström used dietary/caloric restriction (DR) to challenge aging and show that modest DR prolong health and life span and post pone sarcopenia until more advanced age.

Mikael Altu**n** (”Old-Aged Muscle Atrophy: Cellular mechanisms and behavioral consequences”) 2007.
Altun presented an exhaustive study of behavioral impairments that develops in early aging and progresses until endpoint covering testing of >1000 rats, of inbred and outbred rat strains and both sexes. Evidence demonstrates the beneficiary impact of dietary/caloric restriction (DR) as a single intervention in prolonging life-span and retarding the behavioral manifestations of aging, while environmental enrichment alone had a much smaller impact. The data analyses and meta-analysis of previously published behavioral data, validated the

staging protocol used in several of above thesis and, further, provided evidence for a consistency between behaviors recorded in longitudinal studies with those obtained in studies having a cross-sectional design.
In the second part of the thesis Altun studies aging-related changes in regulated proteolysis through the ubiquitin-proteasome system (UPS). The UPS is instrumental for myofibrillar breakdown and thus muscle atrophy. This work was conducted by Altun in Ploegh's and Goldberg's labs at Harvard medical school, Kessler's lab at Oxford University and Ulfhake's lab at KI. Altun was part of a team that develops new active-site probes to label the different catalytic subunits of the proteasome. He applies such probes along with a range of other techniques to assess changes of the UPS during normal aging and aging under DR in the rat. The results show profound dysregulations of the UPS at the end stage of normal aging while DR post pone such changes to more advanced age. He confirm that key E3 ligases are not induced in endpoint sarcopenic muscles and, as a further sign of UPS dysregulation, that dexamethasone known to induce atrophy through induction of E3 ligases fails to do so in senescence.
Using the first generation of in-house spotted gene chips and other techniques, data was presented that a large number of genes, in particular genes coding for proteins related to cellular damage response (redox and DNA damage) and ribosomes, are increased in senescence and that the transcriptional regulations observed co-varied with stage of behavioral impairment.

Andreas Fahlström ("Behavioral Changes and Mechanisms –An Experimental Study on Aging in Rodents") 2011.
Using C57BL/6J male and female mice, Fahlström design and validate a behavioral test battery to assess changes and impairments as they emerge during aging and to what extent they can be counteracted by dietary restriction (DR). Results show that life-span expectation is 29-30 months and similar for both sexes, while modest DR (70%) extends life-span by about 20% to ~36 months. Aging affects a range of behaviors in both sexes of this mouse strain, the most conspicuous alteration was the decline in exploration activity which correlated with impairment of object memory and also poorer acquisition of motor skills. It was proposed that decreased explorative drive may have its origin in the aging-related degenerative processes of central monoaminergic systems (see above under Johnson heading). Further, the gradual decline in behavior responses was shown to be able to predict remaining life-span at least in male mice. Consistent with that a high level of exploratory activity and preserved motor capacity indicated a long post-test survival; males maintained on DR were more successful in these tests than freely fed age-matched males.
The "mutator mouse" is a model on accelerated aging driven by a mutation in the POLGA gene in the C57Bl/6J strain and used here to assess the significance of mitochondrial DNA mutations in the emergence and progression of sarcopenia. The results show that mutator mice are smaller, display decreased longevity, and disclose a mild loss of muscle mass relative to whole body weight at the end point (median survival age) due to the combined effect of fibre atrophy and loss of myofibres. In contrast to WT C57Bl/6J, denervation seems not to contribute to the aging-related muscle wasting observed in the mutator mice.

Paula Malmström ("The Effect of Caloric Restriction on Age-Related Hearing Loss and the Impact of Repeated Sound Exposures") 2013 (together with Mats Ulfendahl).
In this thesis for licentiate degree, evidence from a rat model show that impairment of hearing during aging (presbyacusi) may develop despite only a modest loss of hair cells and no significant reduction in number cochlear sensory neurons The mechanism seems to be degeneration of the microenvironment (stria vascularis; SV) of the organ of Corti. In rats

subjected to dietary restriction, the hearing reflex was preserved in 76% of the cases compared to 15% in freely fed rats. DR maintained rats showed only minimal degeneration in SV while the reduction of hair cells was similar to the freely fed rats.

Claes-Henric Berthold had joined the department in 1959 and as mentioned above under Skoglund he had defended his thesis in 1968. In 1979 he was appointed a professorship in neuroanatomy at Sahlgrenska Akademien, Göteborgs Universitet.
Berthold supervised the following doctoral students at KI to dissertation:
Thomas Carlstedt ”Observations on the morphology at the transition between the peripheral and central nervous system in the cat.” 1977.
Peter Berthold ”Electron Microscopic identification of a dental plaque microorganism - Steptococcus mutans - using immunohistochemistry.” 1978.
Martin Rydmark ”An ultrastructural morphometric analysis of the node of Ranvier in peripheral myelinated nerve fibres of the cat.” 1982.
Håkan Lugnegård ”Ultrastructural morphometric studies on regeneration of the lateral cutaneous sural nerve in the white rat after transection of the sciatic nerve.” 1984.
Ingela Nilsson-Remahl ”An ultrastructural morphometric and reconstructive study of axons and Schwann cells in adult and developing lower lumbar ventral spinal roots of the cat.” 1987.

Claes Hildebrand [5] was one of Skoglunds last PhD students and defended his thesis in 1971, the year before the death of Skoglund. Claes Hildebrand continued his research on the fine structure of the white matter of the central nervous system and became associate professor and lecturer in anatomy. Gradually he expanded his research to include general mechanisms for axonal growth, myelination and breakdown in both the central and peripheral nervous systems (CNS and PNS). He established a number of national and international collaborations. He was a guest researcher at Stanford with Stephen Waxman 1981-82. Hildebrand was an outstanding teacher and exceptionally inspiring supervisor. He had a number of students at KI before he became appointed as Professor of Cell Biology in Linköping in 1986.
His first PhD student Kaj Fried defended his thesis ”Development, Degeneration and Regeneration of Nerve Fibres in the Feline Inferior Alveolar Nerve and Mandibular Incisior Pulps” in 1982. The second student was Mårten Risling who defended his thesis ”Population Changes in Cat Spinal Spinal Roots Following Nerve Injury and During Normal Development” in 1983. Risling had Håkan Aldskogius as co-supervisor. Both Fried and Risling continued as researchers and teachers at KI. A third KI-student, Sten Remahl, continued his thesis work after that Hildebrand had moved to Linköping and defended his thesis ”On myelination in the central nervous system” in 1991. Remahl later became specialist and consultant in clinical neurophysiology. Peter Franson started a PhD project with Hildebrand and continued with Lars-Olov Ronnevie as supervisor after that Hildebrand had moved to Linköping. Franson defended his thesis ”Breakdown and elimination of myelin during Wallerian degeneration in adult cats and kittens” in 1989. Franson became orthopedic surgeon. He also co-authored with Ulrik Kvist at the physiology department a couple of widely used anatomy and physiology books (Anatomi och fysiologi 1&2) for paramedic and nursing students.
Hildebrand had a large number of PhD students in Linköping before he retired in 2005. Unfortunately, he had a major stroke only a few months after his retirement and became unable to continue with research or writing.

Footnote 5: Summarized by Mårten Risling

Gunnar Grant and his group focused on neuroanatomical studies of primary affferent connections to the spinal cord and brainstem, ascending spinal pathways and on development of methods for tracing connections. Then he also discovered what he called transganglionic degeneration, a breakdown of fibres and terminals central to sensory ganglia following peripheral nerve damage. This hitherto overlooked phenomenon turned out to be useful in tracing studies aiming at disclosing central projections of different peripheral nerves. In addition, it had implications for theories on pain.

He had three collaborators joining him from Uppsala, Jörgen Boivie, Håkan Aldskogius and Bo Wiksten. Boivie had graduated in 1970 on a thesis dealing with the diencephalic termination of fibres from the spinal cord and the dorsal column nuclei, using Nauta technique, i.e. silver staining of degenerating fibres and terminals. This technique had also been used by Grant in his thesis in 1962 on the cerebellar projection of fibres from the spinal cord and the external cuneate nucleus in the cat. Boivie´s thesis had given important new information regarding the pain pathways and resulted in an invitation for him a few years later to one of the leading laboratories in the US in this field and to requests for chapters in textbooks. Boivie also became supervisor for Monica Björkeland, who used the same approach as he had done, studying the projections to the midbrain. The title of her thesis, defended in 1984, was ”Anatomical studies of the somatosensory projections to the midbrain from the spinal cord and dorsal column nuclei in the cat”.

In early experiments by Grant and Aldskogius the Nauta method was applied for studying retrograde degeneration of hypoglossal neurons in young kittens, mimicking the modified Gudden method worked out by Brodal. These experiments showed silver impregnated dendrites, cells and axons central to axonal transection and led to the thesis by Aldskogius ”Morphological studies of Wallerian degeneration in the kitten with particular reference to indirect Wallerian degeneration” in 1974. Indirect Wallerian degeneration can be described as a response to axonal damage, affecting primarily the parent cell body and therafter the outgoing part of the axon. Part of the thesis was published as a separate issue of Advances in Anatomy, Embryology and Cell Biology, dealing with his electron microscopic studies of these two types of degeneration in the intramedullary root fibres in the kitten. A characteristic feature of the process of the indirect Wallerian degeneration was found to be the occurrence of a type of microglial cell completely covered by myelin. The findings indicated that these cells reach their position inside myelin by a process of active migration, that they participate in the phagocytosis of degenerating axoplasm, and that they in turn degenerate and are eliminated. A comparison with the situation in direct Wallerian degeneration demonstrated that the same principal ultrastructural changes occur also in this type of degeneration, including the appearance of myelin covered microglial cells. This was all important new information. In two further publications the two types of degeneration were examined following silver impregnation, both at light and electron microscopic level. The granular versus the fibre type of degeneration, characteristic at the light microscopic level, was found compatible with what could be demonstrated at the electron microscopic level and a tentative explanation for the outcome of the two degeneration processes could be given.

Grant had carried out a large number of experiments in kittens with the aim to provoke degeneration in the central branches of primary sensory neurons following peripheral nerve damage. The sciatic nerve was used as a model. The hope was to get a method for tracing. The degenerative process turned out to be too fast, however, and only some few degenerating fibres could be visualized with the available Nauta method. Together with Jan Arvidsson, a trained dentist, he tested the principle of transecting peripheral nerves in the trigeminal system

and this turned out to be successful. This became the start for Arvidsson´s thesis ”Degeneration in trigeminal primary sensory neurons after peripheral nerve transection”, finished in 1978. Some degenerating fibers were detected in kittens, particularly in the older one´s, but prominently in adult rats, which were now used in the experiments. The findings in the kitten material had suggested that the maturation process was crucial. The central projections of the three main branches of the trigeminal nerve were possible to map and their somatotopic organization could be visualized.

As a next step it was of interest to test the spinal level. This led to the thesis by Jan Ygge ”On the organization of spinal primary sensory neurons and their reaction to peripheral nerve injury. Anatomical studies on the thoracic nerve in the rat”, finished in 1983. Here the transganglionic degeneration phenomenon, i.e. degeneration central to the sensory ganglion following peripheral nerve damage, a term introduced by Grant, was confirmed also at the spinal level. Furthermore, based on this, a systematic study was made of the projection patterns for individual thoracic spinal nerve branches in the dorsal horn of the spinal cord. Ygge could demonstrate, in addition, that there was an asymmetry in the thoracic region with regard to the number of ganglion cells in single pairs of ganglia, but that the total number of neurons for all thoracic ganglia on the two sides was markedly similar. By this time also horseradish peroxidase, HRP, had been introduced as a tracer and it had been shown to be transported transganglionically. Grant and his group had contributed to this. Ygge used this for supplementing his previous study with transganglionic degeneration for mapping the central distribution of the different branches of the thoracic nerve. The projections shown by transganglionic transport of HRP were found to be more extensive than those shown by transganglionic degeneration, and a strict somatotopic arrangement could be confirmed, showing longitudinally arranged columns of projections in the spinal dorsal horn.

Transganglionic transport of HRP was also used in the thesis by Carl Molander ”On the organization of spinal cord projections from hindlimb sensory nerves. An experimental study in the rat” in 1986. He examined not only projections from hindlimb nerves but also from cutaneous areas of the foot, using different variants of the method of transganglionic transport of HRP, one of which was with the conjugate with wheat germ agglutinin, WGA. This could be used in much lower concentrations than free HRP, reducing spread of tracer at the site of application. As a basis for these studies a cytoarchitectonic map of the relevant levels of the spinal cord was essential. Therefore, in a special study, such a map was created, using the same principles which had been used by Rexed in 1952 and 1954, studying the cytoarchitecture of the cat´s spinal cord. Projections of cutaneous and muscle sensory nerves, as well as of discrete areas of the hindleg foot were investigated and schematic so-called dorsal view maps of the projections to lamina II, the substantia gelatinosa, of the cutaneous nerves and skin areas were constructed. They showed very precise somatotopically arranged projections and these could be related to the position of the hindlimb during embryogenesis. The thesis also included a study of substance P-, somatostatin-, calcitonin gene related peptide-like immunoreactivity and fluoride resistant acid phosphatase enzyme activity in sensory neurons with projections to cutaneous, muscle and visceral nerves. Except for somatostatin-like immunoreactivity, which could not be demonstrated in visceral sensory neurons, all of the examined activities were found in neurons with projections to cutaneous and muscle nerves, as well as to the visceral splanchnic nerve.

Carlos Rivero-Melián continued studies of spinal cord projections in his thesis ”The spinal cord projections of dorsal roots and peripheral nerves and their overlap. A neuroanatomical study in the rat”, finished in 1993. He developed methods for tracing, using choleragenoid

(CTB) horseradish peroxidase conjugate in studies of distribution of dorsal root fibres in the spinal cord and also applied this in double labelling studies of lumbar dorsal root projections to spinocerebellar cell groups, using Fluoro-Gold as a retrograde tracer from cerebellum. Supplementary information regarding the dendritic trees was gained from cases with cerebellar injections of WGA-HRP. Furthermore, by applying immunocytochemistry in combination with CTB he was able to simultaneously demonstrate central projections of different peripheral nerves. Antiserum against CTB, raised in goat or rabbit was mixed with CTB to obtain two different solutions consisting of rabbit or goat IgG bound to CTB. The different mixtures were subsequently injected into separate nerves. Following transganglionic transport, goat and rabbit IgG were then demonstrated simultaneously in lumbar dorsal root ganglia and in the spinal cord, using an immunocytochemical double-labelling technique. Finally, he used CTB mixed with neuraminidase in experiments with nerve injections and could demonstrate an inclusion of dorsal root ganglion neurons of all sizes and an increased labelling of fibres in laminae I and II_o (outer II) indicating inclusion of small-sized neurons. CTB normally binds to the GM1 ganglioside, present on myelinated fibres, which are not derived from small-sized neurons, and neuraminidase degrades more complex gangliosides to GM1. The findings therefore indicated that more complex gangliosides were present on small-sized neurons projecting to laminae I and II_o. The results were discussed in relation to findings by others claiming sprouting of myelinated fibers in the superficial dorsal horn following sciatic nerve injury.

Brita Robertson carried out a series of studies on the tracer substances wheat germ agglutinin and choleragenoid conjugated to HRP in her thesis ”The neuroanatomical tracers wheat germ agglutinin-horseradish peroxidase and choleragenoid-horseradish peroxidase in primary sensory neurons”, finished in 1992. She found that small calibre somatic primary afferent fibres projecting to lamina I (marginal zone) and lamina II (substantia gelatinosa) of the dorsal horn and the trigeminal nucleus caudalis were more efficiently labelled by WGA-HRP than by B-HRP (CTB-HRP), the binding subunit of choleratoxin, or choleragenoid, conjugated to HRP. In addition to the labelling of terminal areas of small calibre primary afferents in the spinal cord WGA-HRP was also shown to be transferred transneuronally. Coarse calibre primary afferent fibres projecting to the deep dorsal horn, the intermediate grey matter, the ventral horn and the magnocellular zone of the trigeminal nucleus caudalis were more efficiently labelled by B-HRP than by WGA-HRP. Visceral afferent fibres seemed to be as efficiently labelled by WGA-HRP as by B-HRP, although B-HRP resulted in more distinct labelling than WGA-HRP. All of the choleragenoid-immunoreactive dorsal root ganglion (DRG) neurons belonged to the large, light subpopulation, had myelinated fibres and A-fibre conduction velocities. This indicated that B-HRP is a rather selective tracer for this subpopulation of DRG cells, although a number of the large, light cells might not be labelled by B-HRP. The choleragenoid-immunoreactive DRG neurons, furthermore, showed an extensive overlap with neurons immunoreactive to RT97, a monoclonal anti-neurofilament antibody, that labels specifically and exclusively the large light cell population. In contrast to WGA-HRP there were no signs of transneuronal transfer of B-HRP.

In search for alternatives to WGA-HRP as tracer substances for small calibre afferent fibres H. Fredrik Wang studied two different substances in his thesis ”Neuronal tracers for fine caliber spinal primary afferents and their response to peripheral nerve injury” in 1998. Like WGA they were both lectins, glycoproteins of non-immune origin with specific binding to carbohydrate epitopes. The first to be tested was the isolectin B4 from *Griffonia simplicifolia I*, which had been reported to bind to a subpopulation of the rat small-diameter dorsal root ganglion neurons, and to fibres and presumed terminals in laminae I and II of the dorsal horn.

The results obtained showed that B4 binds to a subpopulation of unmyelinated primary afferent neurons and that B4 and B4-HRP can be used as selective transganglionic tracers of this specific cell population. In a second study anterograde transport of B4-HRP was investigated in rat somatic and visceral primary sensory neurons at different spinal levels, using both light and electron microscopy. The results suggested that B4-HRP should be a suitable anterograde tracer of unmyelinated cutaneous and splanchnic but not muscle primary afferent fibres. A third study, in collaboration with MaeJa Park, visiting from the department of anatomy, Kyungpook National University. School of Medicine, Taegu, Korea and Peter Shortland, on visit from the anatomy department, Queen Mary and Westfield College, London dealt with a combined retrograde and transganglionic transport of B-HRP(CTB-HRP), WGA-HRP and B4-HRP in primary afferent neurons innervating the rat urinary bladder. B-HRP was shown to be a more efficient retrograde-transganglionic tracer for pelvic primary afferents from the urinary bladder than WGA-HRP and B4-HRP, but in contrast to somatic nerves, it is transported mainly by unmyelinated fibres in the visceral afferents. A fourth paper dealt with transganglionic transport of the lectin Soybean agglutinin, SBA. It showed that SBA can be used as a transganglionic tracer to label fine calibre primary afferents projecting to laminae I-II of the spinal cord and the gracile nucleus but that it also labels a subpopulation of myelinated afferents. Two final papers dealt with effects of nerve injury and recovery after that, using B4 and SBA, respectively.

Two doctoral theses dealt wih a specific spinocerebellar cell group in the upper cervical spinal cord, C1-C4, the central cervical nucleus, CCN, which is involved in the positioning of the head in relation to the trunk. Bo Wiksten investigated this with three types of techniques in his ”Anatomical studies of the central cervical nucleus and its cerebellar connections in the cat”, 1978. In his first study he used Golgi impregnation methods, the Golgi Cox method for studying cell bodies, the Golgi Kopsch method for demonstrating dendrites, including spines, and the Golgi rapid method for visualizing axons. Two types of neurons, large and small, could be identified. The dendrites of large neurons reach areas outside the CCN, dorsolaterally, laterally and ventrally. These were later shown to receive afferents from, respectively, dorsal roots, ipsi- and contralateral vestibular nuclei. Dendrites of small CCN neurons mainly follow the contour of the CCN. Ramifications of primary dendrites of both large and small neurons have spines. Axons of large neurons reach the anterior commissure. His second study dealt with the cerebellar connections, studied with retrograde transport of horseradish peroxidase. Among the findings were that both the anterior lobe and the posterior vermis receive projections from the CCN and that the axons cross in the anterior commissure of the spinal cord. In the third study the cerebellar connections were investigated, using anterograde transport of tritiated leucine, then a recently adopted tracing method. The axons were found to terminate as mossy fibres in the cerebellar cortex, mainly in lobules I and II and in deep vermal parts of lobules III-VIII. They enterered via the superior cerebellar peduncle. A second thesis on the CCN ”The central cervical nucleus in the rat. Studies on connectivity, function and chemical transmission”, was carried out by Birger Ragnarson. This was published in 1998, twenty years after Wiksten´s thesis. One of his studies was made in collaboration with Seong Joon Ji, visiting from Taegu, South Korea, another one with Matsuo Matsushita, visiting from Tsukuba University, Japan, and still another one in collaboration with Lioudmila Popova, visiting from the Belozersky Institute of Physico-Chemical Biology, Moscow State University and Grigori Orlovsky at the department of neurophysiology. One of the aspects investigated concerned the cerebellar projection of the CCN neurons, their neurophysiology, and by immunocytochemistry at the electron microscopic level, the transmitter content of both neck muscle and vestibular afferents. In a morphological study a correlation was made between CCN afferents, visualized by cholera toxin immunolabelling,

and sagittal Purkinje cell bands revealed by a monoclonal antibody to zebrin I. Although terminals were seen beneath the positive bands, the borders of terminal distribution were not well-defined, and they did not respect the borders of zebrin positive bands. The neurophysiological study led to the conclusion that rat CCN neurons transmit information about position and movement of the head, both in space (vestibular input) and in relation to the trunk (proprioceptive input) to the cerebellum, and that they are not modulated by locomotion. Furthermore, jointly with Brun Ulfhake from the department, also acting as co-supervisor, and with Ole P. Ottersen at the Institute of Basic Medical Sciences in Oslo a series of studies were carried out. Boutons from neck muscle spindle afferents contacting retrogradely labelled CCN neurons and motoneurons were demonstrated to be enriched with glutamate-like immunoreactivity. Choleragenoid, the B-fragment of cholera toxin, CTB, an anterograde, retrograde, and transganglionic neuronal tracer, was shown to be possible to visualize in freeze-substituted Lowicryl HM20^{TM} embedded tissue. Glutamate, AMPA- and NMDA-receptor immunoreactivity in Ia syapses with motoneurons and neurons of the CCN, retrogradely labelled with CTB, was demonstrated in such embedded tissue. Finally, synapses between bulbospinal afferents and CCN neuron were found to be enriched with glutamate-like immunoreactivity and to express AMPA-receptor immunoreactivity postsynaptically.

Spinocerebellar neurons were also the subject of a study on the location of cerebellar projecting neurons within the lumbosacral spinal cord of the cat carried out by Grant, Wiksten and Aldskogius in collaboration with Karen Berkley, visiting from the Department of Psychology, Florida State University, Tallahassee. Here they also made a comparison between retrograde tracing with horseradish peroxidase and retrograde chromatolysis technique and found the former technique to be far superior to the latter.

Spinocerebellar neurons had also been studied in the thesis by Qunyuan Xu**,** a graduate student from Peking, on visit 1981-1983 and 1986-1988, graduating in 1988. The title of his thesis was ”On the organization of axonal projections of spinocerebellar neurons from the lower part of the spinal cord. An experimental anatomical study in the cat.”
A set of different experimental methods, including retrograde degeneration, retrograde labelling with HRP, double labelling with the use of fluorescent tracers applied in the cerebellum and in peripheral nerves, as well as peduncular lesions and/or cordotomies, were used. Their routes of entry into the cerebellum, either via the superior or via the inferior cerebellar peduncle were established for each of the spinocerebellar cell groups. The spinocerebellar fibres in the dorsal and ventral part of the lateral funiculus were related to their respective groups of neurons. Most of the cell groups project to both the anterior lobe and the posterior lobe, including the paramedian lobule. Certain groups project only to the anterior lobe. In groups which project to both areas, many neurons have divergent axon collaterals. Spinocerebellar neurons in lamina IX do not send divergent collaterals to peripheral nerves. Finally, a classification of the spinocerebellar cell groups in the lower spinal cord as to whether they belong to the dorsal or the ventral spinocerebellar tract was proposed.

In addition to the published theses, Grant and his research group contributed with a large number of studies. **Håkan Aldskogius**, who spent a postdoctoral year as a Fogarty Fellow in the US working with Kevin Barron at Albany Medical College, a clinical neurologist scientifically focusing on retrograde changes in the visual system, continued focusing on microglia. Mikael Svensson, his student, presented his thesis on ”Functions of reactive microglial cells following peripheral nerve injury” in 1993 and some of his younger collaborators joined him when he got a professorship at the medical faculty in Uppsala in

1995. Aldskogius also took over as supervisor to several of the doctoral students in Arvidsson´s group at his unexpected death, 48 year´s old, in 1994. One of those was Katarina Bjelke, who defended her thesis in 1997. Some other of the doctoral students joined Aldskogius in Uppsala.

Arvidsson, who had also spent a postdoctoral year in the US, in his case with Steven Gobel at NIH, concentrated on the brainstem projections of the vibrissae system in the rat, demonstrating an organization supplementing what had been demonstrated in the barrel cortex of the rat. In some of those studies he also collaborated with an Austrian anatomist, Kristian Pfaller, who spent some time in Stockholm.

Carl Molander focused on the dynamics of plastic changes in the spinal dorsal horn, following peripheral nerve injury in experimental animals. He got an invitation to University College in London and spent a postdoc year there working in the group of Clifford Woolf, Patrick Wall and Maria Fitzgerald. He became supervisor to the visiting Thai veterinary surgeon Jarin Hongpaisan, who defended his licentiate´s dissertation "Redistribution of c-fos expressing neurons in the rat spinal cord and gracile nucleus after stimulation of the injured sciatic nerve" in 1992. He also took responsibility for a visiting German student, Gunnar Schulte, who also collaborated with Robertson and Grant in a study on effects of nerve injury on δ-opioid receptor and substance P immunoreactivities in the superficial dorsal horn, published in 1999. Schulte later graduated at the department of pharmacology, and he is now professor at the department of physiology and pharmacology. Molander had a very good background when he continued his career as a specialist in medical rehabilitation, with a focus on pain-related problems.

Grant continued his studies on spinocerebellar pathways together with Xu, making use of material that had been produced at the time when Xu had been working on his thesis. They made use of an observation originally made by Robertson that not only cells of origin of spinocerebellar connections and their fibres could be visualized following injections of WGA-HRP at their sites of termination, but that there was an asymmetry with regard to labeled fibres, a difference between the two sides, in cases with unilateral cordotomies at different levels, above the level of the cordotomy. Using this fact they could identify both ventral and dorsal spinocerebellar tract fibres in cases with unilateral cordotomies at different levels, and also relate them to different spinocerebellar cell groups, following injections into either the anterior lobe or the posterior lobe and the paramedian lobule. This illustrated that termination sites could be related not only to cells of origin but also to location of axonal pathways. This was entirely new.

Other studies on ascending spinal pathways dealt with dorsolateral spinal afferents to some medullary sensory nuclei in the cat. They were dealt with in an extensive experimental anatomical investigation together with George Gordon from University Laboratory of Physiology, Oxford, with bilateral visits. Furthermore, on a visit from University of Minnesota, Minneapolis, Glen Giesler joined in a study on the organization of the spinocervicothalamic pathway in the rat. In addition, Gulgun Kayalioglu from Ege University in Izmir, Turkey, visting Krister Kristensson´s laboratory, and Brita Robertson joined in a study on nitric oxide synthase and interferon-γ receptor immunoreactivities in relation to ascending spinal pathways to thalamus, hypothalamus and the periaqueductal grey in the rat.

In collaboration with José Castro-Lopes from Antonio Coimbra´s laboratory in Oporto, visiting the lab, and with Jan Arvidsson, spinal primary afferent connections were studied

with focus on ultrastructural changes of the central scalloped (C_1) primary afferent endings of synaptic glomeruli in the substantia gelatinosa (s.g.) following peripheral nerve damage. Signs of degeneration were found, but no electron-dense degenerative bouton changes characteristic of Wallerian degeneration. Since our previous light microscopic material using the Nauta technique did not show any degeneration in the s.g., the lack of electron-dense degeneration therefore offered an explanation.

Two more studies on primary afferents were carried out jointly with Tomas Hökfelt and his graduate student Chang Xu, his collaborators, and Fredrik Wang. In these studies it was demonstrated that peripheral axotomy induced only very limited sprouting of coarse myelinated afferents into the inner lamina II of the rat spinal cord. This was in contrast to what had been claimed by Clifford Woolf, at Harvard, and co-workers. The explanation was that, as had been suggested in the studies by Rivero-Melián, following nerve damage CTB binds to nonmyelinated fibres, in addition to myelinated fibres.

Other studies on primary afferents concerned the vestibular nerve. Jan Siegborn applied HRP to the transected central end of either of the five nerves the anterior, lateral and posterior ampullar nerve, the utriclar and the saccular nerve in adult cats, by putting a capsule containing 50% HRP to the transected end of the respective nerve for 1 hour. Following transganglionic transport strong labelling was found after about 7 days survival and its distribution was mapped in the different vestibular nuclei. The findings were published in three different papers, the last two with the expert help of Kanoknart Yingcharoen, who had graduated from Mahidol University in Bangkok on a thesis about the nucleus prepositus hypoglossi, but also carried out studies in collaboration with one of the neuroanatomists at the anatomical institute in Oslo. The last paper, dealing with the projections from the saccular nerve, also demonstrated an ordered arrangement of the incoming fibres from all of the five respective components of the vestibular nerve.

Mention should be made also of two studies carried out jointly with Yasuko Kitao, visiting from the Department of Anatomy, School of Medicine, Kanazawa University, Kanazawa, Japan, and with Brita Robertson. By combining immunohistochemistry, using the embryonic stage marker 5-bromo-2´-deoxyuridine (BrdU), a thymidine analogue, with fluorescent tracing, a study was carried out on the neurogenesis of subpopulations of rat lumbar dorsal root ganglion (DRG) neurons projecting to the dorsal column nuclei. The fluorescent tracer Fluoro-Gold (FG) was used for retrograde labeling from the gracile nucleus. The $RT97^+$ neurons were generated on E12-E15, with a peak at E13 and the $B4^+$ neurons on E13-E16, with a peak at E14. The overall pattern of neurogenesis of the DRG neurons showed that the $RT97^+$ neurons, the large light population, were produced prior to the $B4^+$ neurons, the small dark neurons, giving rise to unmyelinated fibres. A second study dealt with the proliferation patterns of DRG neurons of cutaneous, muscle and visceral nerves, using FG as the tracer. DRG neurons of muscle and intercostal nerves were generated early, with peaks at E13, those of cutaneous and visceral afferent nerves later, with a peak at E14. The temporal differences were related in the cell size spectrum, the muscle nerve having a greater proportion of large neurons compared to the cutaneous nerves. The findings added to previous knowledge regarding the sequence of development of different DRG phenotypes.

Finally, with the support by the laboratory of Grant and collaborators three studies were carried out by Oliver T. Phillipson from Bristol, UK. They dealt with the dopamine cell groups in the ventral tegmental area of Tsai, VTA, and the interfascicular nucleus in the rat. He used Golgi techniques, Nissl and myelin staining, glyoxylic acid-fluorescence

histochemistry for catecholamine neurons and retrograde tracing for studies of afferent connections to these areas. All these studies were published in the Journal of Comparative Neurology in 1979 and contributed with important new inforrmation.

Lars-Gösta Elfvin focused on ultrastructural studies of the autonomic nervous sytem. In addition to many original publications he became editor of the book ”Autonomic ganglia”, which was published in 1983. This comprehensive volume contained contributions from nineteen specialists with reviews dealing with the structure, function and development of autonomic ganglia. In addition he became supervisor to three graduate students. Carl-Johan Dalsgaard finished his thesis in 1982, dealing with ”Central and peripheral connections of sympathetic ganglia” and using retrograde axonal tracing technique and immunohistochemistry”. Catarina Andersson Forsman defended her thesis ”Ultrastructural studies on membranes in sympathetic ganglia, enteric ganglia and smooth muscle cells” in 1985. Here she applied freeze-fracture technique which made it possible to disclose membrane structures that she was focused to reveal. Björn Lindh´s dissertation took place in 1989 and dealt with ”Immunohistochemical analyses of transmitters and peptides in mammalian autonomic and sensory neurons and their projections.”

Dalsgaard soon became supervisor to Anders Haegerstrand, whose thesis ”Sensory neuropeptides in inflammation and cell proliferation” was finished in 1990.

This was followed by Lars Bengtsson´s thesis ”Lining of cardiovascular prosthetic materials with cultured adult human endothelium” in 1992.

In 1979 the associate professorships held by Elfvin and Grant were converted to regular professorships.
Elfvin became emeritus professor in 1994 and Grant in 1997. Both of them continued their research after that. Sadly, however, Elfvin was affected by Parkinson´s disease and as a cruel consequence of a fall accident half a year before he died he became paralyzed in all his four limbs.
Grant devoted much time also to the field of history of neuroscience and published several papers in this area in international journals, including one publication on Nobel laureates in neuroscience, which was later published on the website for the Nobel assembly.

Kinesiology group – with **Jan Ekholm**

A couple of years after professor Sven Carlsöö’s retirement, Jan Ekholm formed another research group focusing on movement analysis (kinesiology) of human beings using a combination of methods of biomechanics and analysis of activation of muscles – electromyography (EMG). This topic area was called functional anatomy.
A basic question at the time was the magnitude of load that occurred on different structures of the musculoskeletal system during human movements, e.g. during work tasks. A background factor then was the increasing incidence of disability related to work environmental factors and an increasing societal interest in ergonomics. The main activities of the group will here be presented using information of the PhD theses produced; each thesis is based on 5-6 international publications.

A first PhD thesis from the group appeared 1984 with Gunnar Nemeth: ”On hip and lumbar biomechanics - a study of joint load and muscular activity”. Basic biomechanics parameters were mapped, such as maximum hip extensor muscular moment in Nm as a function of hip

angle and as a function of degree of knee flexion, loading moment cased by body segments, and in vivo moment arm lengths for hip extensor muscles at different angles of hip flexion. The loading moment of force about the hip and lumbo-sacral joints during lifting techniques was calculated at regular intervals during the lifts, using a computerized sagittal model. Rising exercises were studied with the same methods.

With a similar basic question a thesis on the biomechanics of the knee was presented by Ralph Nisell: ”On the biomechanics of the knee. A study of joint and muscle load with applications in ergonomics, orthopaedics and rehabilitation" (1985). To quantify the force magnitudes acting in the tibio-femoral and patello-femoral joints, a local biomechanical model of the knee was developed using a combination of cadaver knee dissections and lateral knee radiographs of healthy subjects. The model was applied to different work postures. Also, in this thesis a study of joint load during parallel squat in powerlifting was included, enabling calculations of in vivo strength limit of the human knee extensor tendon. A world top class power lifter was injured during a championship while squatting with a burden of 382.5 kg. In the deepest squatting position (“thighs horizontal”) both quadriceps tendons ruptured completely and he fell to the floor. As all lifts were videotaped at the competition, basic parameters of this lift were available, making it possible to estimate the quadriceps force at the time of rupture – between 10.9 kN and 18.3 kN in each quadriceps tendon.

In the treatment of shoulder problems exercise is a common step. In Karin Harms-Ringdahl’s thesis (1986) “On assessment of shoulder exercise and load-elicited pain in the cervical spine”, factors related to physiotherapeutic exercises were described using biomechanical analysis of load and EMG. In addition, in four of the included articles, pain provoked by extreme joint positions were analysed; one describes the intensity and character of pain elicited by maintained extreme flexion position of the lower-cervical-upper-thoracic spine in healthy subjects showing that this posture, resembling the posture in some work, caused pain in all subjects, increasing in intensity with time and had a primary location in the dorsal part of the lower cervical and upper thoracic spine and upper part of shoulder regions.

Ulf P Arborelius presented 1986 his thesis: “On assessment of musculoskeletal load with biomechanical models and EMG - applications on shoulder during therapeutic exercise and standing work.” The aim was to investigate how biomechanical models together with electromyography can be used as a guide to principles underlying the generation of load in living human joint and muscle structures. The purpose was also to use the shoulder joint and shoulder muscles as an application area, investigating shoulder load during lifting, standing work with hand-held tool, and exercise. Among other things, a computerized system for dynamic whole body calculations (six joints) in one plane was designed which can calculate forces and moments transmitted between segments, and can analyse the influence of dynamic factors, burden, other external forces body size or weight. It can calculate loading joint moments in occupational situations.

Cycling is often recommended as exercise and, at the time, little research had focused on mechanical joint load. The general aim of Mats Ericson’s thesis (1986) “On the biomechanics of cycling. A study of joint and muscle load during exercise on bicycle ergometer” was to quantify the load induced in the lower limb joints and muscles during exercise on a bicycle ergometer and to study how these loads were affected by adjustments of the bicycle ergometer or the cycling technique used. The forces, load moments and muscular power output on and about the hip, knee and ankle joints during cycling were determined using cine-film, pedal force measurements and biomechanical calculations based upon static and dynamic

mechanics. The muscular activity of eleven lower limb muscles was recorded and quantified using EMG. The hip extensor muscles produced 27%, hip flexors 4%, knee extensors 39%, knee flexors 10% and ankle plantar flexors 20% of the total positive mechanical work.
The main purpose of Ola Svensson's thesis (1987) "On quantification of muscular load during standing work - a biomechanical study." was to present a measure of mechanical load representing all major muscle groups during standing work. Irrespective of what method is used, it is of value to relate the demand from the work load to the capacity of the worker. Various methods exist for this. Comparing the load moments about joints in absolute values is of limited practical use. Also, it is difficult to interpret direct comparison of the load moment for a given joint at different joint angles. If, however, the load moment about a joint axis is divided by the counteracting maximum muscular moment ("strength") at the same joint angle, a ratio is created and in this thesis termed the muscular strength utilisation ratio (MUR). To examine the applicability of the MUR concept, the loads on the muscle groups of the ankle, knee, hip, back and shoulders during lifting with straight and with flexed knees were quantified and compared using the method described.

With the increasing incidence of neck-and-shoulder pain related to work environment as background, Kristina Schüldt 1988 presented her thesis "On neck muscle activity and load reduction in sitting postures. An electromyographic and biomechanical study with applications in ergonomics and rehabilitation". The general aim was to study the effect of posture changes and use of ergonomic aids on the level of muscular activity in posterior neck muscles in sitting work postures. Three of the studies are methodological, aiming at further mapping of the functional anatomy of posterior neck muscles, using surface EMG in different loading test situations and neck spine positions. Surface EMG recordings were made from 1) cervical erector spinae at the level of vertebra C 2-3 covered by the upper part of trapezius, 2) splenius, 3) levator scapulae, 4) trapezius pars descendens, 5) trapezius pars transversa covering supraspinatus, 6) thoracic erector spinae covered by the aponeurosis of the rhomboids, 7) sternocleidmastoid muscle. The biomechanics and muscular function of the cervical spine were studied when skilled women workers simulated standardized simulated electromechanical assembly work in eight sitting work postures. The posture with the trunk slightly inclined backward and neck vertical gave the lowest activity levels. It was concluded that work postures can be optimized to diminish neck muscle load. The ergonomic aids elbow support and arm suspension were studied during the same work cycle and both aids reduced normalized EMG levels.

In 1992 Eva Hammarskjöld presented her thesis " Exposure to cold, vibration or muscular fatigue - its effect on the reproducibility of work movements. A study of EMG amplitudes, perceived exertion and quality in carpenters´ work with hand tools". Construction workers are often exposed to cooling of hands or frequent use of vibrating tools, circumstances claimed to provoke accident risks. The aim of the studies was to find a model for analysing the reproducibility of well-known tasks and, with this, to analyse the reproducibility of the same tasks after exposure to cold, vibration or muscular fatigue. Experienced carpenters repeated common nailing, sawing and screwdriving tasks. Later, performance of the same tasks after exposure to hand-arm vibration, hand cooling or arm–shoulder-fatiguing arm-cranking was studied. All the exposures resulted in increased activity in trapezius pars descendens. The work pace was not affected by vibration, was somewhat slower after cooling and instable after muscular fatigue. The quality of the work ("errors") was affected only after muscular fatigue.

In the orthopaedic surgeon Lars Weidenhielm's thesis "Knee osteoarthrosis. Aspects on clinical symptoms, corrective surgery, leg alignment and knee load." (1992), studies of biomechanical loads on joints pre- and post-surgery are presented (in collaboration with Ola Svensson)

In 1995 Per Wretenberg presented a thesis on the kinesiology of rising with Ulf P Arborelius as supervisor. The title of this thesis was "On leg extension: mechanical load and muscular action during rising with and without technical aid and during exercise."

Arborelius was also supervisor for a master´s thesis in 1997 for Feng Yi: "A study on the effect of arm support used during sedentary work on arm posture, mechanical load and muscular activity."

In conclusion:
This presentation of the department of anatomy summarizes what happened from the early 1960ies until the fusion of the department into the newly created department of neuroscience in 1993 and the continued research activities in the different research groups after that. A description is given of the changes which took place as a result of the increase in the number of students in the early 1970ies, including a move of the teaching localities into the newly created Berzelius laboratory and an expansion of the localities for research. A detailed description is given for each of the research groups, their focuses and the theses presented by each of their graduate students.