The Department of Medical Epidemiology and Biostatistics (MEB)

A brief account of the department's origin at Uppsala University and development at KI 1997-2018

by

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Content:

1. Summary

This brief account of the history of the Department of Medical Epidemiology and Biostatistics (MEB) was chiefly compiled by Hans-Olov Adami, who was the founder and *primus motor* during the formative years. Colleagues, who influenced the development and the directions taken, have contributed to the narrative. They are named within brackets after the respective sections.

The history of MEB is unusual – probably unique. What subsequently was to become MEB grew following no a priori plan from a one-man firm to a department employing about 250 people in about three decades. During the embryonic phase, a group of clinical practitioners worked together within the Department of Surgery at Uppsala University. The main thrust was on cancer – treatment, causes and control – and the scientific approach was epidemiological. In 1990, this group became formally autonomous although it remained administratively a part of the Department of Surgery until 1994 when Uppsala University established a new Department of Cancer Epidemiology.

Following continued growth, the entire department moved to KI in 1997. To distinguish it from other epidemiologically oriented groups at KI, and to reflect its broadening scope, it was renamed the Department of Medical Epidemiology (MEP). The move allowed and stimulated not only a remarkable acceleration of the department's expansion but also further increased diversity of the research portfolio. Fruitful interactions with the KI leadership and other departments both at the KI Campus and at the hospital fueled the process and fertilized the research. Important landmarks included integration of the Swedish Twin Registry, establishment of an academic biostatistics group - justifying a change in our name to the Department of Medical Epidemiology and Biostatistics (MEB) – and dramatic professionalization of our IT-infrastructure. This department is now in 2018 the biggest academic unit for epidemiologic and biostatistical research in Scandinavia and probably one of the biggest in Europe, still under vital expansion, scientifically prolific and well-funded.

(Hans-Olov Adami, Olof Nyrén)

2. The birth of MEB 1980-1989

In 1975, Adami returned to his alma mater Uppsala University in order to finish his surgical training with the traditional academic components and with an ambition to pursue a PhD. At the time, the research portfolio within the Surgical Department was limited – traditionally dominated by experimental research on animals – and epidemiology was largely unknown both within the Surgical Department and the Medical School at large except for limited activities within the Department of Social Medicine. By a simple co-incidence, Adami's PhD work became a case-control study of breast cancer – by today's standards hopelessly underpowered – funded through a contract from the NCI to the Cytology Department aimed to investigate "Possible correlations between epidemiology and morphology in breast cancer". He defended his thesis in January 1978 and became docent of surgery one year later. Although he continued the training in various surgical sub-disciplines through 1986, scholarly work became increasingly attractive and the power of epidemiologic theory and study design fascinating.

In the beginning of the 1980s, a growing number of clinical practitioners began to enthusiastically work together on an increasingly diverse research portfolio. With visionary foresight, Ingemar Persson, an OBGYN specialist, initiated a prospective study of menopausal hormone treatment already during his residency, before joining the university department. This unique study, supported by the Medical Products Agency, was the foundation for several theses studying endometrial cancer, breast cancer as well as cardiovascular and other outcomes. It also catalyzed early collaborations with the National Cancer Institute at the NIH in the US. Lars Holmberg joined the group as a PhD-student already during his residency at Falun Central Hospital before moving to Uppsala in 1986. Another research group ran a series of randomized trials on peptic ulcer disease whilst Olof Nyrén pursued his thesis work on non-ulcer dyspepsia. In collaboration with the Swedish Cancer Registry at the National Board of Health and Welfare and the NCI, we also undertook the first large-scale survival analyses of cancer in Sweden. Cancer epidemiologic research, in its broadest sense, remained, however, the backbone of this informal but growing research group.

Part of the growing Uppsala Cancer Epidemiology Unit in the late 1980s, still hosted in the Surgical Out-patient Department. Standing from left: Christer Ljungman, Lars Holmberg, Ingemar Persson, Tord Naessén, Hans-Olov Adami, Magnus Thörn, Britt Gustavsson McCurdy, Torgny Nordén, Eva Ahlstad, Anne Jennische, and furthest to the right Lars-Erik Hansson. Sitting: Johanna Adami, Alicja Wolk and Ulla Bergholm.

Needless to say, the expanding activities needed a physical infrastructure which unglamorously began in the late 1970s with a part-time secretary and a second-hand electric typewriter. We did, however, successively expand the staff to ultimately include three secretaries and one computer programmer. Until 1990, the activities remained physically localized to one corner of the Surgical Out-Patient Department. Through fine support from the Professor of Surgery Lars Thorén we invaded small territories such as a small space, originally built for gurneys, by putting up new walls. The researchers, however, had to resort to their typically jam-packed clinical office space. At Uppsala University's Department of Statistics, Professor Reinhold Bergström became the group's anchor-point in its increasingly audacious excursions into new statistical territories. This was also a period of rapid technical development. We were proud to receive our first fax

machine. And even prouder when we purchased a used word processor, a big and rather noisy Scribona machine, which revolutionized the processing of manuscripts, grant applications and more.

Because the in-flow of new collaborators, PhD-students, staff, and grants from the Swedish Cancer Society as well as the NCI continued, it became increasingly clear during the late 1980s that the Surgical Out-Patient Department would ultimately – and probably soon – be unable to accommodate our needs for physical space. The sustainability of this unexpectedly growing research group improved in 1986 when the Swedish Cancer Society made a nation-wide announcement for a newly established senior research position in cancer epidemiology and appointed Adami. We therefore interacted with the supportive director of the University Hospital Gudmar Lundqvist and found a house centrally located in the hospital area that underwent a profound renovation.

(Hans-Olov Adami, Olof Nyrén)

3. Growth and recognition: 1990-1996

The move in 1990 into our first tailor-made premises in an old three-story house centrally located in the hospital area was a landmark. The house itself, now demolished since years, had a long history, only partly known by us; it had served as a personnel canteen, an orthopedic ward and as lecture halls. More importantly for our scholarly work, the move into this spacious, functional and esthetically attractive (we employed our own interior designer) premises coincided with two developments. Firstly, we were established as an economically and administratively autonomous unit. Still formally within the Department of Surgery, we were in practice completely independent. This presaged the establishment in 1994 of a new Department of Cancer Epidemiology within the Medical School at Uppsala University. Secondly, the Swedish Cancer Society considered their investments in cancer epidemiology successful, and decided to fund a national tenured professorship in cancer epidemiology. Because the Swedish Cancer Society is formally a private charity, the appointment process was handled by the Swedish Research Council. Following nation-wide competition, Adami was appointed by the government in the spring of 1990. Through this appointment, the unit had its first academic position with sustainable funding. The “national” character of this position

later turned out to be crucial because it allowed the appointee to negotiate with any university in Sweden.

During the subsequent years, growth continued on all levels. The core group comprised outstanding scholars with a long clinical background. Ingemar Persson, Olof Nyrén, Lars Holmberg, Anders Ekbom and later Sven Cnattingius were pioneers. Not only clinical practitioners joined us to pursue their PhD work but increasingly also outstanding medical students. From the National Board of Health and Welfare, Pär Sparén, Head of the National Cancer Registry, joined the Department already in the 1980s and was followed later by Paul Blomquist. Ultimately four PhD students also took a year off to pursue a Master of Public Health at the Harvard School of Public Health.

John Baron, a distinguished epidemiologist and professor from Dartmouth University in the US, fertilized our research activities during a one-year sabbatical in the unit. And Leif Gustafsson, with a background in the technical sciences and particularly in dynamic modeling, began his landmark studies on the natural history of cervical cancer and the impact of PAP-smear screening domestically and internationally. This was indeed the beginning of an ever-expanding research program on the prevention of cervical cancer still continuing today under the leadership of Pär Sparén and Joakim Dillner. But already in the early 1990s, we were privileged to establish a deep collaboration with Jan Pontén, Professor of Pathology and Chairman of the Swedish Cancer Society. With support from the NIH, this collaboration allowed us to initiate large-scale studies on the role of human papilloma virus in the etiology of cervical cancer and its precursors.

Concomitantly, the network of collaborations outside of Uppsala University grew. Leif Bergkvist, subsequently promoted to Professor of Surgery, remained based at Västerås Central Hospital both before and after his thesis work. And strong links, viable still today, were established already in the late 1980s with Örebro University, particularly with the Department of Urology (Jan-Erik Johansson, Swen-Olof Andersson) and Surgery (Göran Liljegren). Collaboration with the US Center for Disease Control (CDC) in Atlanta began when Peter Layde in 1984 was the opponent on Ingemar Persson's thesis work, which allowed two graduate students (Anders Ekbom and Göran Lundegårdh) to pursue part of their thesis work in the late 1980s in Atlanta. The collaboration with CDC continued into the early 1990s.

Gradually, however, links to the Epidemiology Program at the National Cancer Institute (NCI) in Bethesda, US strengthened with a rich exchange of people, priceless financial support through intramural contracts and an impressive scientific output, chiefly based on record linkage studies using Swedish health databases; this internationally unique resource had until then been used predominantly for administrative purposes. Fueled by Adami's appointment as adjunct professor in the Department of Epidemiology at Harvard School of Public Health, links to Harvard also began in 1992; they have continued and grown ever since with an impact that can only be underestimated.

In the early 1990s, we also began to successfully apply for large grants (RO1s) from the NCI at the National Institutes of Health (NIH). This was indeed a prerequisite for the increasingly large epidemiologic studies that were developed. Ultimately, by the end of the 1990s, we had launched nation-wide (or large regional) case-control studies of cancers of the esophagus, stomach, anus, kidney, prostate, breast, endometrium, ovary as well as NHL and Hodgkin's lymphomas.

Due to the continuing growth it became gradually obvious that we would soon grow out of our convivial premises in the hospital area. The crowding did indeed become so substantial that we initiated discussions with the hospital director sometime in 1994. One year later, when about 80 individuals were linked part-time or full-time to the Department, we moved to beautifully designed and spacious premises in a new house neighboring the Pathology Department just south of the hospital area, beautifully decorated with contemporary art purchased during a euphoric one-day tour through leading Stockholm art galleries under specialist guiding. We consulted with the same interior designer and the esthetic value of our premises were indeed unique for an academic environment.

The Uppsala Cancer Epidemiology Department gathered in the lecture hall of our neighboring Pathology Department after our move to new premises in the Glunten area. In the first row we find among others: Ylva Trolle and Cecilia Magnusson. In the second/third row: Anders Ekbom, Paul Blomqvist, Johan Askling, Sven Cnattingius, Ann Almqvist, Hans-Olov Adami, Jan Pontén and Pär Sparén. Standing in the middle of the next row: Reinhold Bergström, Ingemar Persson and Alicja Wolk. And in the back: Michael Fored, Olof Nyrén, Mats Lambe och further to the right Elisabete Weiderpass.

4. The move to Karolinska Institutet in 1997

Uppsala University was the alma mater for virtually all senior researchers and the majority of graduate students. And most of us lived in Uppsala since decades and were firmly anchored in the city. Therefore, it was frustrating and concerning to gradually realize that the academic environment in Uppsala was suboptimal although we were scientifically prolific and probably one of the largest recipients of external grants, both domestic and from the NIH. We had essentially no contacts with the leadership of the Medical School, no representation in its governance and no financial support from the budget of the Medical School. The financial discrimination was because the Department was classified as clinical, while it was given no access to the ALF funding that sustained all

other clinical departments. Therefore, compared to all other departments, the net-flow of money was reversed and went from the Department to the Medical School rather than from the Medical School to the Department. This hopeless situation led us to consider Karolinska Institutet as an alternative and probably more supportive academic home.

On December 13, 1993, Adami had a secret lunch in a booth of a Stockholm restaurant with Erling Norrby, Dean of the Medical Faculty at KI, and Ulrik Ringborg, Prefect at Radiumhemmet. The purpose was to explore interests and opportunities to move the Department. Because mutual interest was confirmed, numerous interactions followed during the spring of 1994. And these negotiations were openly disclosed to all members of the Department. We did indeed charter a bus allowing all interested scholars, students and staff to visit the Karolinska Hospital, meet with Ulrik Ringborg and acquaint themselves with the potential premises at the Norrbacka Institutet with a wonderful southern view over Stockholm.

Following continued discussions and interactions both within the Department and with the KI leadership Adami met the Dean at KI again in May 1994 now together with both Ulrik Ringborg and Bertil Hamberger, a professor of surgery. The meeting made it clear beyond any doubt that the KI leadership was not well coordinated and that the conditions for a move of an entire department were so vague that a decision would have been irresponsible. Another important lesson was learned during this half year long process, namely that the negotiations for a move with such drastic social and other consequences for a large group of people cannot be openly pursued; understandably, it would cause uncertainty, concern and worries.

Because the circumstances in Uppsala did not improve, informal discussions about a move continued, notably among senior faculty members. This led to a new and this time confidential contact with the KI leadership in the summer of 1996 when Hans Wigzell, an old friend of Adami, had become Rector and Jan Lindsten Dean of the faculty. Adami and Nyrén, Deputy Prefect, led these negotiations that now proceeded smoothly and successfully. The KI leadership did indeed accommodate all our major requirements including to become a new department located at the KI Campus, to appoint all members of the department to positions identical to that at Uppsala University, to

receive initial financial support before becoming fully integrated into the KI financial system and, not least important, to offer premises that would accommodate our ever-expanding needs.

In the mid fall of 1996, the negotiations – undertaken in strict confidence both at the department in Uppsala and at KI – were successfully concluded. The fundamental prerequisites for a move, which would clearly be an unprecedented event in Swedish academia were two-fold: Adami's professorship was national and the entire Department was run on external grants. At this stage, all senior researchers in the Department decided to lock themselves up like cardinals during one day, forced to come out with a decision to move or not to move. We all realized that this was probably the last chance during the foreseeable future to make this decision.

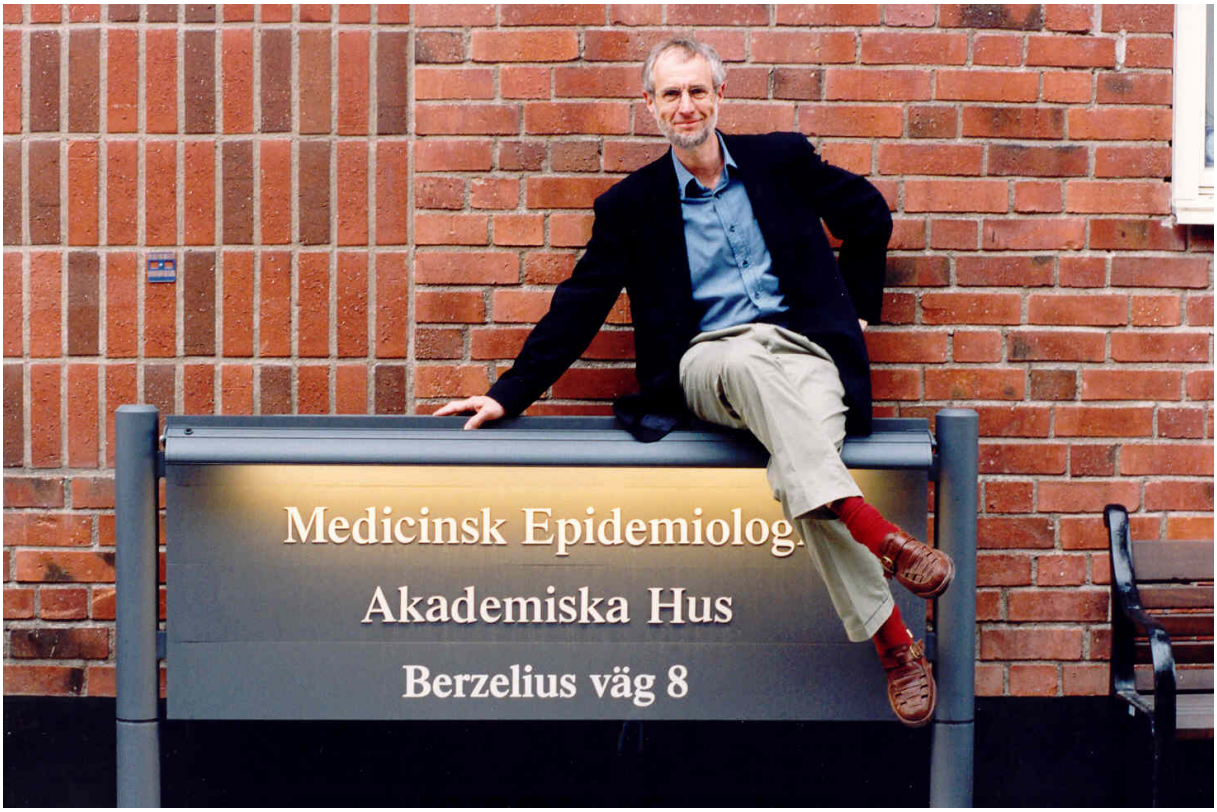
The meeting took place in a historical location close to the main university building on November 21, 1996. Following one day of constructive discussions and careful scrutinization of the prerequisites the group, comprising 13 individuals, voted in unison for a move to Karolinska Institutet. The same evening, Adami tried in vain to meet the Dean of the Medical Faculty to convey the message and dictated a letter to him and to the university Rektor Stig Strömholm in which he exhaustively laid out the arguments for our decision to move. Through channels that remain enigmatic, this long document was leaked to the local newspaper Uppsala Nya Tidning.

The following day was explosive. Our move was extensively featured in the newspaper. Completely surprisingly, however, the university and the leadership of the Medical Faculty reacted with fury and aggressiveness. Adami was fired as Prefect invoking conflict of interest due to the new KI connection. The university was unwilling or unable to accept that the only justification for our move, at the expense of substantial social sacrifices, was to find a richer and more supportive academic environment. Although it is beyond the scope of this historical account to review this drama in detail, an intense debate followed in the local newspaper which provided unanimous support for us in a main editorial entitled "Adami's lesson". KI was immensely helpful in arranging transferal of our research grants. And Hans Wigzell interacted with the government which appointed Adami as professor and prefect at KI from March 1, 1997 although the move was planned to take place immediately after that summer.

5. The seamless integration at KI: 1997-2002

Liquidation of the entire academic department at Uppsala University was not a trivial process. In advance, a meeting with the entire personnel had been announced in the morning following the decision to move. The message was obviously dramatic but received with impressive tolerance and understanding; everyone seemed to respect that the only driving force was the ambition to pursue cutting-edge research which, in the long-term, would be hard or impossible in an unsupportive academic environment with vulnerable funding that relied entirely on soft money. At the time, about 80 people were employed but only Adami had secured funding through his tenured professorship. For various reasons, chiefly social, 40 people ultimately had to quit their positions and stay in Uppsala whilst the remaining 40, including all doctoral students and all senior faculty except Lars Holmberg were willing and able to join in the move to KI. Transferal of all research grants was complicated too although strongly facilitated by KI:s University Director Rune Fransson. Some official statements from the Uppsala University Rector were, however, so concerning and provocative to our main funder, NIH in the US, that Adami had to visit Bethesda in order to explain the situation.

Whilst the long-term plan was to accommodate the need for space through construction of new buildings, the short-term plan was to move into Georg Klein's renowned Tumor Biology Building at the KI Campus. During the spring of 1997, when this house underwent renovation and transformation from premises designed for experimental laboratory research to "dry" epidemiologic research, we were offered preliminary premises on the top floor in a neighboring building. These premises were used during the spring chiefly by Adami and Nyrén when they spent a few days per week to prepare the move of the entire Department after the summer.



Hans-Olov Adami outside Georg Klein's former Tumor Biology Department, now thoroughly renovated for epidemiologic research.

We will never forget the first visit when keys to our premises were to be handed over and we expected to meet a janitor. Instead, when we reached the top floor, Rector Hans Wigzell, Dean Jan Lindsten and Director Rune Fransson were waiting for us with a flower – a movingly warm welcome and manifestation of outstanding academic leadership. When Hans Wigzell's success as Rector was shortly later featured in the Science Magazine, recruitment of the Uppsala Department was described as "his boldest move" (1). Needless to say, we read this with pride.

The move of the entire Department after the summer of 1997 was an exciting but uneventful undertaking flavored by optimism. The integration at KI was indeed seamless, all doctoral students became registered at KI, teaching activities continued, senior faculty enjoyed the Campus atmosphere and we hired a young economist as our first administrative head of the Department; she was succeeded by Birgitta Svensson who sadly left us prematurely due a fulminant illness. Computer programming and IT-infrastructure were initially an Achilles' Heel because the market for programmers was

incredibly competitive at the time, some of them were unable to join in the move whilst others had an entirely different academic background.

Whilst the Department had remained an enclave within Uppsala University, intense academic interactions began immediately at KI. During the monthly meetings between the KI leadership and all Department Prefects, about 25 at the time, Hans Wigzell convinced us that the sum of KI was greater than its components. Concomitantly, the Campus Departments still had regular faculty meetings which also facilitated integration and helped us become acquainted with the function and the ethos of our new environment. Already in the late 1997, Adami was elected member of the Nobel Assembly – and during the three first years also the Nobel Committee – which provided another stimulating aspect of academic life at KI.

A group of outstanding senior scholars, all with a strong clinical background, joined the move to KI, but they remained lectors whilst Adami was holding the only professorial position. Around this time, however, a new law made individual promotions possible. As a corollary, Ingemar Persson, Olof Nyrén, Anders Ekbom and Sven Cnattingius received their well-deserved promotion to tenured full professor which represented a quantum leap in the academic structure of the Department. Alicja Wolk, a nutritional epidemiologist from Warsaw, had joined the Department already in Uppsala, she had developed the dietary component of virtually all etiologic research projects and also became promoted to full professor. A few years later, Wolk decided to move with her group of doctoral students to the Institute of Environmental Medicine (IMM) where she could work more autonomously. Already before Wolk left MEP for IMM a remarkable move in the opposite direction took place when Nancy Pedersen decided to transfer the prestigious Swedish Twin Registry, largest in world, from IMM to MEP. This move also allowed us to foster the promotion of Pedersen to a full professor and Paul Lichtenstein to lector and some years later to full professor.

MEP and its predecessor in Uppsala had a rather unique organization (or lack thereof) and financial structure; there were no formal research groups and all resources were pooled into a joint economy. This structure had four important goals. Firstly, to allow every scholar to put together his or her dream team for any particular project without crossing any borders of administrative or financial nature. Secondly, pooling of resources

was a prerequisite for development of the infrastructure which began during the early years and has continued ever since. Hence, we had cultivated growing groups of highly competent research administrators, administrators, data collectors, IT-staff and biobankers.

Gradually, however, the IT-group did not only grow but also became highly professional with the hiring av Jan-Eric Litton as Professor of Biomedical Computing Technology as a landmark. Thirdly, the Department had muscles enough to launch expensive preparatory work spearheading grand studies that could only find support outside of Sweden. This was beautifully exemplified by a series of nation-wide case-control studies of upper GI cancers, hopelessly rejected by Swedish funding agencies but subsequently funded through R01's at NIH's National Cancer Institute. Finally, the structure of MEB was intended to foster an ethos of integration, solidarity and intense collaborations. Unfortunately, the pliability and boldness described above is becoming less and less appreciated in today's academic and public governance.

Because expansion of the Department continued, it became apparent that our needs could not be accommodated in the former Tumor Biology Building while we waited for the construction of our tailor-made buildings around the former Department of Anatomy and Histology to be completed. The KI leadership was extraordinary receptive to our needs and decided to put up two stories of barracks just outside of the Tumor Biology building with a skyway connecting the barracks with the Tumor Biology Building. But within a few years, also these barracks were so crowded that a third floor had to be added. In retrospect, it is almost enigmatic that the integration at KI and the continued expansion into new premises could take place essentially without any friction between the Department and the KI leadership, perhaps with one exception: It was hard to cover rental costs from the soft money we received, notably from domestic funding sources.

(Hans-Olov Adami, Olof Nyrén)

6. Biostatistics – a strategic investment

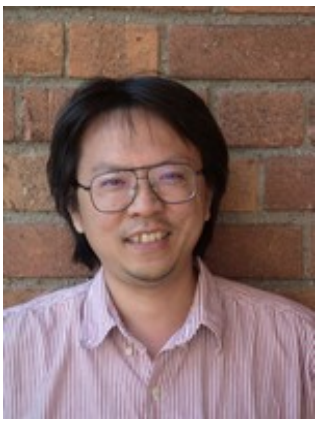
Swedish medical research – basic and particularly clinical and epidemiological – has suffered substantially from the lack of heavy weight biostatistical support. It is indeed enigmatic that all medical schools in the country seem to readily accept the need for

several dozens of clinical disciplines to cover the entire spectrum of human diseases. But at the same time, they expect scholars in medicine to resume responsibility for biostatistical analyses notwithstanding the fact that this is a complex academic discipline under rapid expansion. As mentioned previously, we had the extreme privilege to collaborate with Reinhold Bergström in the Department of Statistics in Uppsala, formally Professor of Econometrics. Bergström was intellectually brilliant, absorbed biostatistical theory and methods seemingly instantly, had unimaginable working capacity and always remained curious to squeeze out all important information from any new study. His contributions were acknowledged through an Honorary Doctorate in Medicine at Uppsala University and already from the late 1980s he was formally employed 50%. Our immensely productive collaboration continued after the move to KI although Bergström undertook most of the work in Uppsala with only occasional visits to Stockholm. Unfortunately, Bergström suffered from a malignant disease that ultimately ended his life prematurely around Midsummer in 1999.

Already before Bergström left us in deep sorrow, we acknowledged that high-level biostatistical support would become another Achilles' Heel of future work at MEP. This insight led to fruitful interactions with Juni Palmgren, Professor of Biostatistics at the Stockholm University Department of Mathematics. Reflecting our joint ambition to establish the first ever academic entity for biostatistical research in Sweden within MEB we announced a professorship in biostatistics domestically and internationally. The yield of applicants was unimpressive, reflecting both that the recruitment base was essentially non-existing within Sweden and that starting from scratch with no critical mass was unattractive for successful and advanced international biostatisticians. At the end of this process, Palmgren and Adami interviewed the two top candidates but felt forced at the end of the day to interrupt the process and start all over.

At this critical stage, the KI leadership was again supportive and foresightful because they decided to provide secured funding during five years for a strategic professorship. And a new international announcement with successful use of Palmgren's impressive international network generated a much stronger team of applicants. The outcome was extraordinary successful because we were able to hire Yudi Pawitan, professor at Cork

University in Ireland and his spouse Marie Reilly, also promoted to full professor rather soon.



Yudi Pawitan

Marie Reilly

Outside of Karolinska Institutet the lack of academic biostatistics in the country was soon recognized. Palmgren was successful in securing two large framework grants in applied mathematics from the Foundation for Strategic Research 2003-2009. These grants covered 10 graduate students in statistical science supervised by the seniors in the newly formed biostatistics group at MEB and by the Dept of Mathematical Statistics at Stockholm University. Around the same time, Palmgren together with professor Stephen Lagakos at the Harvard School of Public Health, secured STINT funding for an exchange program in Biostatistics, allowing six of the PhD students from Stockholm to take part in regular courses at Harvard, and students from Harvard to visit MEB resulting in a generally vivid exchange. The strategic funding from KI together with the external grants allowed a flying start for Biostatistics research and graduate education at MEB.

In parallel, the Applied Biostatistics group at MEB proved its importance. From the start in 1997 the MEB Applied Biostatistics group focused on service and development work, with central steering and funding by MEB Faculty. Research and applied work in Biostatistics quickly became intertwined, with an intimate connection to epidemiological research, which in turn has contributed to the large number of publications from MEB in high ranked journals and to a high citation index.

Biostatisticians at MEB have been thoroughly aware of the development in genetics, bioinformatics, e-science and data science and have formed a broad network of collaborations at KI, SciLifeLab and with other universities in Stockholm and abroad. The Biostatistics group has arranged a number of high-profile international symposia in statistical methodology with medical applications and in methodological aspects of register-based research. For over a decade the group led by professor Rino Bellocco in Milan (also lector at MEB) has contributed to an Annual International Summer School in Italy, run together with the Harvard School of Public Health.

The Biostatistics group at MEB is still in 2018 unique in Swedish academia, both in size and scientific achievement. The group has attracted new leaders at the lector level with a supervisory role. Today the group is successful in securing its own research grants for biostatistics research and graduate education. In short – due to the early boost, Biostatistics at MEB is thriving. In 2018 the group comprises around 50 persons of whom close to 20 are PhD students, often recruited from departments of statistics or mathematical statistics or from universities of technology and funded by external grants.

In the KI External Research Assessment (ERA) evaluation in 2010 it was stated that the biostatistics group at MEB has the potential to contribute more to education in biostatistics at KI – also at a more advanced level in parity with international education in medical biostatistics. Up to now, however, the outspoken ambition at MEB to set up an international Master Program in Biostatistics has been postponed at KI centrally.

Besides the early professors Palmgren, Pawitan and Reilly one new professor, Paul Dickman, has been appointed and one new professorship in biostatistics is under international evaluation. Because Palmgren, Pawitan and Reilly will all be retired before the end of 2019 it is crucial to add competence in the most senior layer. In order to secure sustainability and competence in statistical science it is important that the group maintains a culture of publishing in high ranked biostatistical journals – a feature which needs constant reinforcement. While a focus on theoretical epidemiology is important for practical work, all levels of biostatistics research and graduate education needs to build on a thorough understanding of the foundation of statistical theory.

(Juni Palmgren, Hans-Olov Adami)

7. IT-infrastructure becoming a backbone of MEB research

Computers, algorithms, and software was not keeping up with the exponentially rising tide of data in epidemiology at MEB. The raw material in epidemiological research is the huge data sets that we spend enormous sums of money and effort to collect. The addition of Jan-Eric Litton to MEB in April 2001 – and promotion in 2002 to professor of biomedical computing technology, the first of its kind in Sweden – started the building of Karolinska Institutet's most extensive computing facilities for research.

Database infrastructure has become a critical component for competitive life sciences research and discovery. Epidemiological research, particularly longitudinal studies that may run for several generations, demands completely new methods and systems to handle the gathering and storage of huge quantities of information. The lack of robust and well-defined database strategies makes sophisticated data analysis cumbersome and expensive. Modern epidemiological database design had indeed to rethink the entire concept of data modeling and cohorts. While the concepts of data warehousing and decision support had been around for decades, the availability of cheap disk storage made large-scale data warehousing a reality for epidemiology and biostatistics today.

To handle these growing datasets, a Storage Area Network (SAN) was implemented including fast computers supported by an IBM SUR (Shared University Research Program) grant in 2003. Via the SUR grant we received four IBM pSeries servers and a FastT 700/900 SAN storage solution and supporting software.

The computing group at MEB now started transforming the large cohorts in a more professional, uniform, and sustainable way. In 2003 the various databases at MEB contained complex information, often longitudinal, from over 6 million individuals. An important agreement was also made with the leading database software company Oracle and KI, and the fist professional database manger (Jenny Carlsson) was hired, the first step to MEBs Database administration policy.

The SUR-grant also entailed a strategic relationship between IBM Svenska AB and KI in the creation of a joint research initiative in the life sciences. One of the outcomes was to construction the first BIMS (Biobank information Management system) in 2004. BIMS implements important advancements in the definition, structure, and standardization of

information that has been gathered from a multitude of sources, such as population-based registries, biobanks, patient records, and large-scale molecular measurements. At this time, no system similar to BIMS, designed for epidemiologic research, had been described in the scientific literature. 2013-2017 this platform was further developed to a Database Infrastructure for Large Prospective Cohorts in Sweden called myResearch, an information service infrastructure project, financed by the Swedish Research Council, and affiliated to MEB.

In 2002 we proposed a new database network called Hub and Spoke, and implemented in the EU project GenomEUtwin 2002-2007. MEB was one of the tree Centers of Excellence in Genomics in the 5th EU Framework Program aimed to connect 600.000 twin pairs in Europe. Eight twin cohorts, including the Swedish Twin Registry, used a federated database. The phenotype hub was the computer network at MEB and the genotype hubs were at the Finnish Genome Center in Helsinki and the Molecular Medicine Group in Uppsala. Within this setting, the researchers communicate effortlessly with the twin cohort data, collected and updated over the past 40 years, stored in the systematic, harmonised way making the effort less dependent on individual data collectors.

Systematic collection of demographic and lifestyle data is central in any epidemiological study. The traditionally used methods such as face-to-face and telephone interviews as well as paper-questionnaires were increasingly failing to produce good qualitative results within financially feasible limits. A tool that was better suited for the present dynamic populations was needed and the Internet presented a powerful alternative for the collection of data: e-epidemiology was born. Two Ph.D. students (Alexandra Ekman and Christin Bexelius) did their theses in e-epidemiology between 2002 – 2009 with Litton as the main supervisor. We define e-epidemiology, as the science underlying the acquisition, maintenance and application of epidemiological information using digital media such as the Internet, mobile phones, digital paper, digital TV. e-epidemiology also refers to the large-scale epidemiological studies that are increasingly conducted through distributed global collaborations enabled by the Internet. In 2005 we concluded that web-based questionnaires are feasible tool for data collection in large population based epidemiological studies in Sweden.

In 2007, MEB – in collaboration with the Swedish Institute for Infectious Disease Control (SMI) – initiated a new type of study for influenza surveillance. In a pilot study, a new population-based network of sentinel individuals was established for monitoring infectious disease occurrences in the Swedish population. The aim of this study was to detect early influenza epidemics/pandemics. The infrastructure in the system consisted of cost and time effective information and telecommunication technologies, such as Interactive Voice Response and web portals.

During Karolinska Institutet's 200 year's anniversary in 2010, MEB organized a series of lectures in e-epidemiology under the theme: "Adapting epidemiological methods for the 21st century". Litton was appointed BBMRI-ERIC's first Director General on 22 January 2014 - 1 August 2017, building up one of the largest infra-structure for Health in Europe. Before appointed as the Director General for BBMRI-ERIC, Litton was the Executive Director and head of one of the largest medical infrastructure in Sweden – BBMRI.se (The Biobanking and Molecular Resource Infrastructure of Sweden) with MEB as the home. He also coordinated the Nordic BBMRI (Denmark, Sweden, Norway, Finland, Island, Faroe Island and Estonia) between 2009-2013.

(Jan-Eric Litton, Hans-Olov Adami)

Following extensive renovation and expansion, the former buildings hosting the Departments of Anatomy and Histology were renamed to Wargentin. Pehr Wilhelm Wargentin (1717-1783) a contemporary with Carl von Linné was a secretary at the Royal Academy of Sciences during 34 years and a pioneer in population statistics which was developed in Sweden earlier than in other European countries.

8. The Wargentin Building: 2002-2005

In 2002, the last phase of MEB's integration at KI became completed. The KI leadership had fulfilled all commitments made before we decided to move from Uppsala. And the historic buildings that in the past hosted the Departments of Anatomy and Histology had been renovated and completed with the construction of a new five-story building with beautiful offices, numerous meeting rooms, a basement that could accommodate the need to securely store servers and other computer facilities. The centrally located open light atrium (Ljusgården) was a uniquely attractive airy space that connected the buildings. These buildings also accommodated the expanding KI Biobank for which MEB was in charge. In addition, we had neighboring lecture halls and a suite of guest rooms which facilitated accommodation of visiting scholars and our first post docs from Harvard (Lorelei Mucci and Ellen Chang) and Iceland (Unnur Waldimarsdottir) who spent part-time at MEB.

Part of the MEB staff two years after our move to the Wargentin buildings.

Important expansion of senior faculty took place during these years. Already before the move, we successfully recruited Per Hall, an experienced oncologist and cancer epidemiologist from Radiumhemmet. Hall has played a pivot role for further development of MEB. Beginning also before the move to Wargentin, Henrik Grönberg, newly appointed Professor of Oncology at Umeå University, started to spend part-time at

MEB where he became a driving force, particularly for our research program on the genetics of prostate cancer. After the move, we announced a professorship in cancer epidemiology, Grönberg was appointed for the position, quit his professorship in Umeå and moved full-time to MEB.

Early after our move from Uppsala, a committee was appointed, charged with the mission to establish a satellite epidemiologic unit at the Hospital to support clinical research. This led to a professorship for which Anders Ekbom successfully applied, and to the establishment of KEP (Clinical Epidemiology), a unit that absorbed numerous former graduates at MEB and played a pivotal role in developing the remarkably successful 20-week training program in clinical epidemiology. Hence, KEP became an enormously successful investment and has kept strengthening the methodology of clinical research. The collaboration between MEB and KEP has not been intense but continued on many levels without friction.

Without going into detail, the infrastructure of MEB kept expanding both qualitatively and quantitatively. The IT-group grew and became more specialized, including a group of professional database administrators. The group of data collectors, chiefly nurses, were a prerequisite for the expanding field work and data collection activities. Unlike virtually all other academic departments, MEB invested in highly qualified secretaries working closely with senior faculty members and playing a pivot role to foster an effective management of the Department.

Adami had remained Prefect of the Department formally from 1994 in Uppsala but declined to be re-appointed for another period when approached in the fall of 2005. His goal was to counteract inbreeding, foster renewal and secure more time for his own research. Hence, Nancy Pedersen was elected new Prefect from January 1, 2006 starting a new era in the development of MEB. A few months later, Adami was unexpectedly approached by Harvard University in Boston and asked to become Chair (Prefect) of the Department of Epidemiology at the Harvard School of Public Health (2). He took up this position in early 2007 and lived there for five and half years.

9. Consolidation and growth during 2006-2017

After Adami left MEB, the Pedersen and her executive group started the task of meeting the demands of the KI administrative structure (which focused on individual research groups rather than having a flat organization such as MEB) and at the same time fostering the development of the department in the same ethos as before. When Pedersen became the Vice Dean of Research at KI in 2008, Henrik Grönberg became the prefect. Paul Lichtenstein followed Grönberg as the prefect in 2014. MEB's economy stabilized and improved despite expansion of the infrastructure (including a growing applied biostatistics group, professional IT, database and data collection). Staff meetings moved from once a month in the Ljusgården held by the administrative head, to weekly held by the prefect with the Ljusgården filled to the brim. A "MEBer of the Year" award was instituted to celebrate those members of the department who contributed to the MEB spirit.

During this period, MEB made the strategic decision to focus on early career positions. The number of post docs at MEB went from 2-3 to the current 24 in 2018, all of whom are supported by external grants. In a strategic move, MEB also established centrally financed Assistant Professor (forskningsassistant) positions, for those young scientists who have completed their postdoc, and are not yet eligible for a senior researcher or lecturer position. MEB finances approximately 2 of these positions each year (for a 2 + 2 yrs appointment). Through the years, 19 young scientists have held this position, many of whom have continued as senior researchers at MEB, and currently (2018), 15 are at MEB.

The scientific focus of the department diversified, with an expanding inclusion of genetic and molecular epidemiology across various disorder oriented areas. Other than cancer epidemiology, psychiatric and infectious disease epi as well as biostatistics grew. New professors were appointed each year between 2006 and 2016, in genetic epidemiology (Paul Lichtenstein), psychiatric epidemiology (Christina Hultman), medical epidemiology (Pär Sparén, Weimin Ye, Elisabethe Weiderpass Vainio, Mats Lambe), cancer epidemiology with emphasis on genetic epidemiology (Kamila Czene), clinical epidemiology (Catarina Almqvist Malmros, Jonas Ludvigsson), infectious disease epidemiology (Joakim Dillner, Johan Gieseke and Karl Ekdahl (adjunct)), biostatistics (Paul Dickman) and, for a short period, cardiovascular epidemiology (Erik Ingelsson).

In 2015, MEB was fortunate to become the scientific home of Cynthia Bulik (professor of epidemiology of eating disorders) and Patrick F. Sullivan (professor of psychiatric genetics), both of whom were awarded prestigious international research professorships funded for 10 year by the Swedish Research Council. MEB also has been priviledged to have several guest professors, starting with Juni Palmgren (biostatistics), and more recently Niklas Långström, Mikael Landén, Unnur Valdimarsdottír, Henrik Larsson, and Brian D'Onofrio (psychiatric epidemiology or epidemiology). MEB is also proud to have two of KI's honorary doctorates affiliated: Professor Juni Palmgren and Professor Margaret Gatz.

A 2018 gathering of part of the MEB staff in our Atrium Ljusgården.

With this impressive collection of scientific capital, MEB has also become the home of several centers of excellence. MEB hosts the translational research environment CRisP. Financed by the Swedish Research Council through a 10-year Linnaeus grant, CRisP was established in 2008 based on a shared vision of decreased breast and prostate cancer mortality through individualized risk prediction and prevention. The Center for Eating Disorders Innovation (CEDI), is dedicated to applying novel and emerging methodologies and technologies to elucidate causal mechanisms underlying eating disorders. Catarina Almqvist Malmros is responsible for the Swedish Research Council SIMSAM (Swedish Initiative for Research on Microdata in the Social and Medical Sciences) node "SIMSAM MEB family design". And, since 2010, MEB is one of the key departments in the Strategic

Research Program in Epidemiology (SfoEpi), of which Nancy Pedersen is the Director, as well as the Strategic Research Program in Cancer (StratCan), of which Kamila Czene is the Co-Director.

Three important KI Core Facilities are at MEB. Founded in the 1960's, the Swedish Twin Registry, is the largest of its kind and has become an invaluable resource for medical research. Since 2017 it is an "infrastructure of national importance" supported by the Swedish Research Council. Through MEB's pioneering efforts in 2004, KI Biobank, a modern and high-tech infrastructure for pre-analytical handling, storage and distribution of human biological samples, was established. KI Biobank is an essential core facility for many of the large cohorts with sample collections at KI, including KARMA, STHLM2, STHLM3, and LifeGene (which is now a core facility), all at MEB.

Since 2009, MEB also plays a prominent role in undergraduate and graduate education at KI. The department is responsible for the scientific education, called "scientific development" (VetU) in the medical program at Karolinska Institutet. VetU introduces students to scientific thinking and a scientific approach that modern physicians need in their daily work. Within VetU is course Scientific Methodology in Medicine and the Degree Project in Medicine. MEB is also responsible for the course Differential Psychology within the psychology program at KI. Finally, MEB is responsible for several of the courses, particularly those in biostatistics, in the doctoral program in epidemiology at KI.

MEB has become known at KI not only as an outlier in terms of organizational structure and climate, but through its scientific excellence. All @MEB are proud of the "MEB spirit", which fosters collaboration rather than competition. This is reflected by a number of parameters: the positive reviews in the graduate student exit polls, the ironic difficulties in finding internal representation on student committees (every collaborates with everyone and hence in COI), success in gaining external grants, and scientific productivity.

(Nancy Pedersen)

10. Prefects/Heads of department at MEB

Hans-Olov Adami

Uppsala 1994-1996
KI 1997-2005

Nancy Pedersen

2006-2007

Henrik Grönberg

2008-2013

Paul Lichtenstein

2014-2017

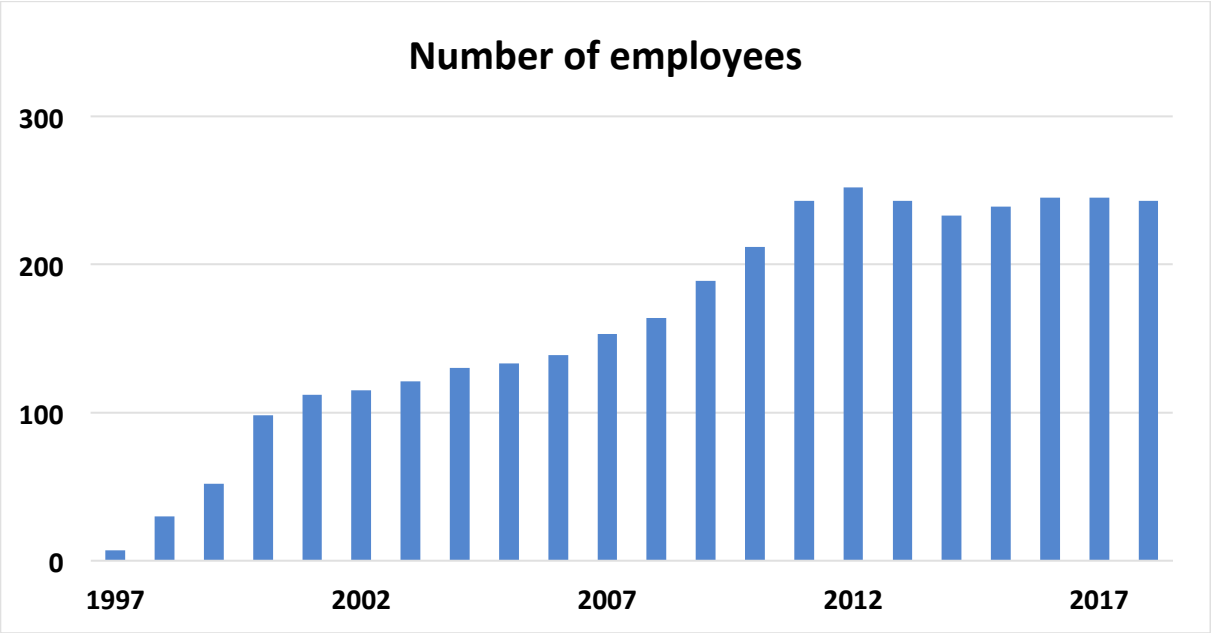
Per Hall and Kamila Czene, acting prefects

2017-2018

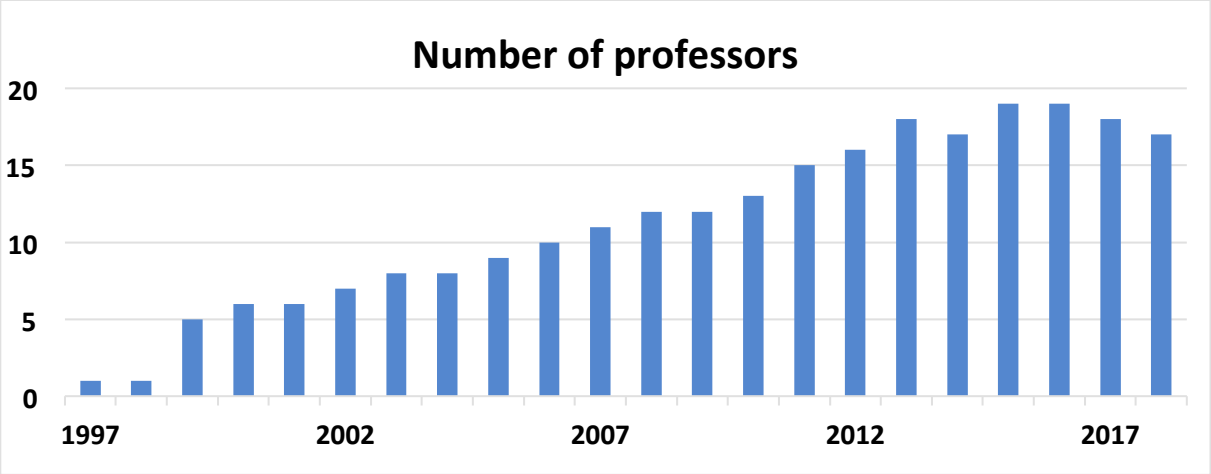
Kristina Johnell

2019-

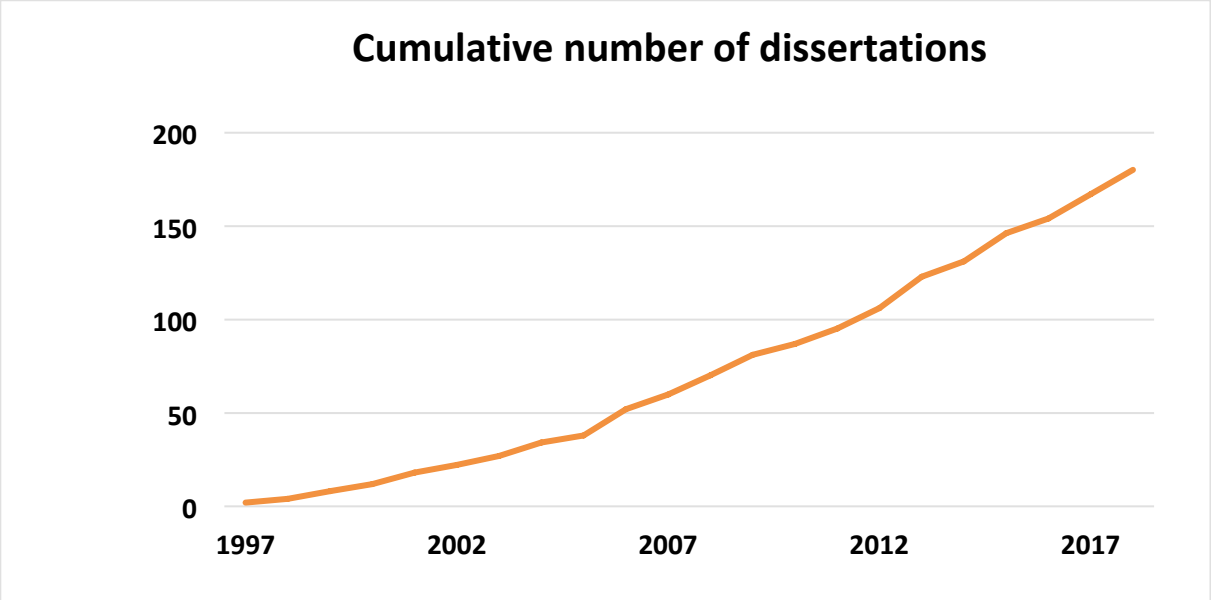
11. MEB in numbers



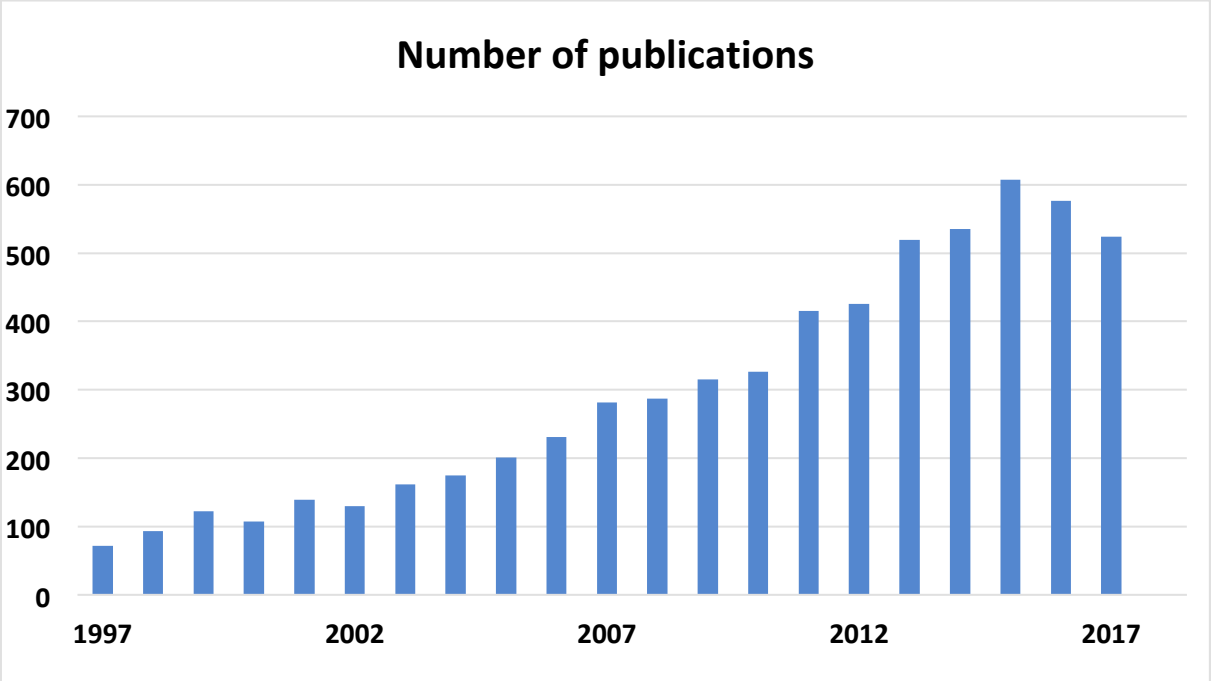
The department employed about 80 people at the time when we decided to move from Uppsala to KI in 1997. Of these, around 40 joined in the move. The department then grew quickly during the first decade. But since around 2011, the number of employees has remained fairly stable at about 250.



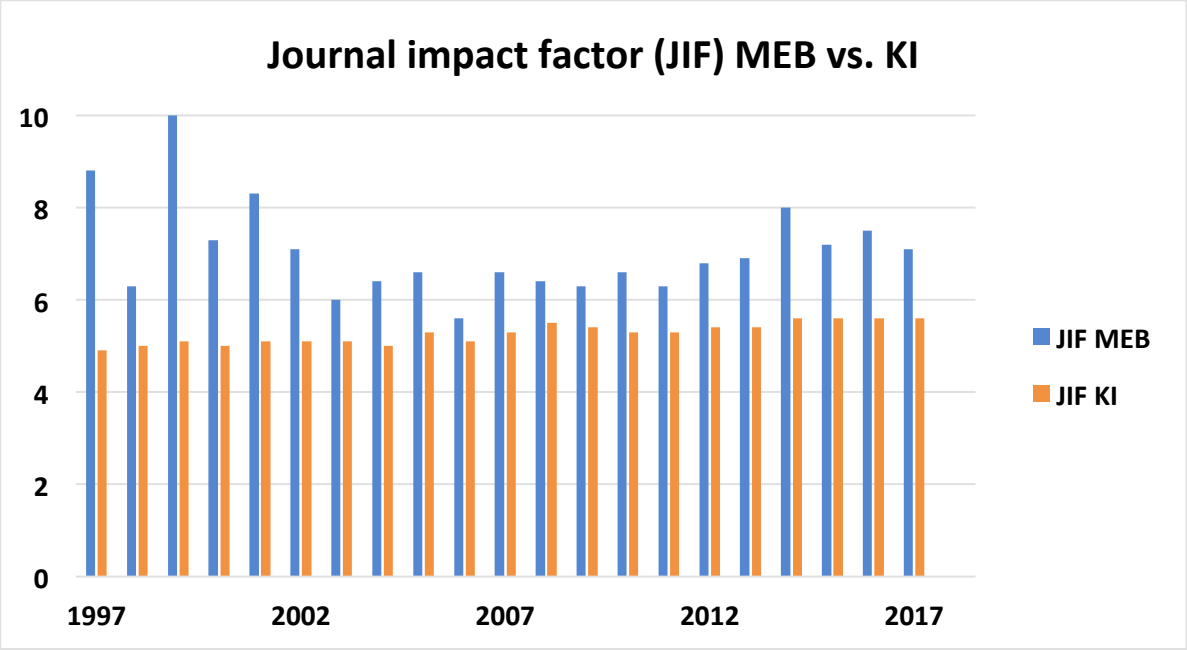
Until 1999 Adami remained the only full professor at the department. Subsequently, the number increased continuously and has now remained in the range 15 to 20 since 2011. In addition, MEB has had a number of prominent international scholars as Foreign Adjunct and Visiting Professors.



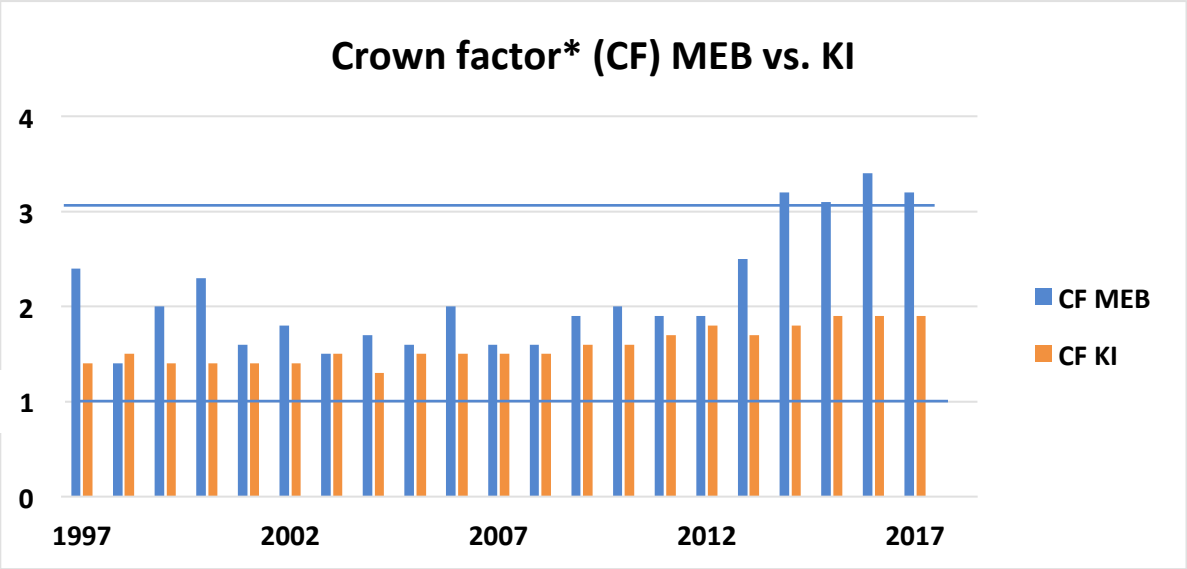
During the early years at KI, approximately two doctoral students defended their thesis annually. By 2018, the annual number is around 15 and cumulative number has reached 180. And if we include also thesis defended during our early years in Uppsala the department has produced around 200 doctoral thesis by 2018.



During the first years at KI, MEB published barely a hundred scientific papers annually. Since then, the department has experienced an about 5-fold increase, now with an annual number of publications in the range of 500 to 600.



The mean annual impact factor in the journals in which MEB research was published has – with some fluctuations – been in the range of 6 to 8 and consistently higher than the mean at KI which has merely been around 5.



With a few exceptions MEB has had a higher annual crown factor than KI at large. This discrepancy has become substantial and consistent since 2013. In 2017, KI exceeded the international average by 90% whilst MEBs CF was 220% higher than the international average.

**The average field normalized citation score is calculated for all verified publications excluding publication year equal to the present or the last year. The world average is about 1,0.*

12. Sources of information

1. Jocelyn Kaiser et al. Working Sweden's Population Gold Mine. Science 2001: Vol. 293, Issue 5539, pp. 2375
2. Adami's recruitment to Harvard was featured in Nature Magazine Published in Nature 444, 120 (1 November 2006).
3. Ever since November 1994, a Department Newsletter has been punctually published, initially with 10 issues per year and more lately less frequently but with elegant typography. The Newsletter has kept its initial name Praesepe and all issues are available at: http://intra.meb.ki.se/Socialeventsimages/Praesepe/Pages/default.aspx.