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## ESN Bachelard Award Lecture

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# ESN - a key start to my scientific and academic career

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First of all I would like to express my sincere thanks for the honour to receive the Herman Bachelard award. It is a great honour for me, not at least because Herman Bachelard was one of my first senior international neurochemist advisors, which meant a lot to me. I think it was almost the first time we met when I told him that I found it difficult to summarise/write an abstract to my presentation and/or scientific article in 200 words. I had so much to tell. His answer was clear - if you cannot give your message in 200 words you have not defined your scientific question. This has been advice I have carried as a researcher and forwarded to my students and postdocs.

I would have loved to stand here and give a review of the field of gangliosides. However, my active research period ended in 2006 when I became the Vice-

Chancellor at the University of Gothenburg. So I will instead share my views on research development, particularly in Neurochemistry, since the end of 1970 with a focus on glycosphingolipids and the key role that ESN has played for my career as scientist and as academic leader.

To be exposed to critical but supporting advice and guidance (apart from that of the supervisor) from senior scientists that, with an open mind, invite you to the international research network is crucial in one's research development. Given the possibility to attend international meetings in the neurochemistry field, ESN and ISN, and be exposed to a prominent research network early in my scientific career, as PhD Student and post-doc, gave me knowledge, new perspectives and contacts outside my "home" research environment.

Not only attending but also, as a young researcher, to be invited to present your research at international conferences gives you a platform to start collaborations with new research groups. And not least it is a merit for your research career. The senior community of researchers have a responsibility to give attention to young talented and qualified researchers.

ESN (and also ISN and its sister organisations) draw, and still do, attention to young researchers, which is recognized and hopefully appreciated by both young and senior researchers. As I recall during my active time as a researcher most international meetings acknowledged young researchers mainly in the poster session and the interest from more senior researchers was often indifferent. We have all been beginners in the field.

In 1982, when I was a postdoc with Professor Victor Ginsburg at NIH I was honoured with the ESN Young Lectureship Award – "structure and function of gangliosides" and invited to the ESN meeting in Taormina, Sicily, Italy. So – now I am back again in Italy receiving a second award from the Society).

At this meeting I am impressed by the fact that there have been 4 sessions with focus on young researchers: *i, my first conference- how to make the most of it; ii, how to make a living with a PhD; iii, young scientist award lectures; and iv, young members' symposia.*

International experience through a post-doc stay was gained when I started my career and it is still an important merit but also valuable for your own development as an independent researcher. The international meetings increase your possibility to be recognized and get personal contacts with research groups where you might do your post-doc period.

I knew this and I was privileged to have a very creative post-doc stay with Professor Victor Ginsburg at NIH. Not only did I develop my research competence in the lab but also gained experience of another research environment and how to handle life in a new country. It was a successful period and important for my independence in a research career. I brought my 6 year old daughter but not my husband and it was a tough time for the family. This leads to the following message:

There is a need to recognize gender and social perspectives and to find alternative routes for the classical 2-3 year stay as a post-doc. I am convinced that many talented young scientists, particularly women, do not have the possibilities to go abroad for longer periods for family and/or economic reasons. Maybe we lose talented and highly devoted scientists this way.

A long time stay abroad is not necessary to develop your research and start collaborations. I have met top researchers that have developed their international networks and collaborations through shorter visit periods but with longstanding contacts. I take the opportunity to bring this up at this occasion and am hoping for common efforts from the senior research community to support next generation researchers through rethinking of the merit and funding system. The limits have been apparent when working as Vice-Chancellor and not least as President of the International Association of Universities (IAU).

Why did I choose the scientific path?

It was not an early decision of mine although my friends and parents later told me that they were not surprised, as they had always found me driven by curiosity and the need to challenge myself in finding answers and solutions. I started my university studies at the Chalmers University of Technology in Göteborg. I studied chemistry and did my Masters thesis at the Department of Clinical Nutrition – my first contact with medical science.

When I finished my Masters the job market even for engineers was limited. Moreover, at that time the employer with no hesitation told a female applicant that they preferred a younger man to a young woman with the same qualifications. The reason behind this general statement was that young women were getting pregnant and thus a bad investment for the company. I am sorry to say that the scientific world at that time and unfortunately also today carry this view. Hopefully the ongoing trend, at least in some countries, that also men take child care responsibility will change the view and also attract the best scientists (with social responsibilities). In many countries the students, PhD students not least in medicine, are women.

With an impossible job market and a growing interest for life science I studied biology and was offered a PhD position in 1974 at the Department of Neurochemistry at the University of Gothenburg with Professor Lars Svennerholm as the head and supervisor. My introduction to neurochemistry, at that time a small and for many unknown field in science, was at the front line.

Svennerholm was a member of the ‘‘Problem Commission on Neurochemistry’’, which was created in 1959 with the objective of creating a focus for neurochemical research. The first symposium on neurochemistry in 1961 had the title ‘‘Brain Lipids, lipoproteins and the Leucodystrophies’’, reflecting that neurochemistry started out with a focus on lipids. As a PhD student, I got involved in the Swedish meeting in 1975 preceding the formation of ESN, which was a fantastic introduction to the “big shots”.

Professor Lars Svennerholm was one of the pioneers in the field of glycosphingolipids and lipidoses and he was the first to describe glycosphingolipids with sialic acids – the gangliosides. It was therefore no surprise that gangliosides became the molecules of my career as a researcher. The title of my thesis was “Structure and Function of Gangliosides” – I need to say that structural analysis of gangliosides really was the main focus while findings related to their function were limited. I would say that their function still today to a large extent remains unclear. Looking into the titles of the more recent publications on glycosphingolipid and gangliosides similar questions arise – there is always more to do.

When I started my PhD in 1974 methods for isolation and separation of individual gangliosides needed to be developed to allow determination of the more complex structures in the next step. The lipid storage diseases, GM1 and GM2 gangliosidoses, (Fabry, Gaucher, Krabbe…) enabled isolation of those gangliosides as they were highly enriched in tissues facilitating their extraction, purification and thereby structure determination. Autopsy materials from healthy control individuals and from with those genetic disease were essential. At the time animal models were only those in with natural genetic modifications, like some dogs with lipidoses, but there were no transgenic mouse models.

Focusing your research time on methodological development meant time-consuming work with lots of trial and error and with no scientific publications along the way. It would have been difficult with the current financing system, with strong demand for publications, to get new funding and merits. However, at the time, methodological work paid off as a merit for funding and career. The Swedish research foundation even gave extra merit to publications on methodological development.

As a benefit of the methodological work I continued with publications on identification and structural determination of gangliosides and other glycosphingolipids but, to be honest, with jealous feelings that others in the field could benefit without having spent the time for such methodological development.

Today, similar objections are heard related to the development of open data - who will take the time and efforts to collect data and take responsibility for the quality when it becomes available for “everyone”. However, for science development in all countries and for transmission to society, open access and open data is a positive move but the concerns have to be handled.

A concern today, I know I share with many other scientists, is that the personal value and merit of methodological development is low. This might lead to consequences such as quality aspects and limitations of scientific development.

There is no question that there has been enormous technology development, resulting in much fantastic equipment to be applied in basic science and in clinical practice. In neuroscience new imaging techniques, including targeting molecules, MR to mention a few, with several Nobel prizes along the road.

However, although highly advanced technical equipment has revolutionised the field of science, and not least in neurobiology/neurochemistry, methodology in science comprises so many more steps, selection of material, procedure for collecting materials, extraction and isolation of molecules from tissues and body fluids, and not least quality assurance of the assay methods used.

One example is related to materials and material collection: analyses of markers in cerebrospinal fluid have become a tool in diagnosis and treatment follow-up in e.g. neurodegenerative processes, inflammation, etc with Alzheimer’s disease being a good example.

As there is a gradient in the CSF, the volume tapped from the individual is essential to make comparisons. This was something that was recognized and taken into account at the beginning of CSF analyses. Standardisation of tap procedures followed. However, in the lipid and glycosphingolipid fields, another complicating factor became apparent.

In glass tubes, most often used worldwide in such analyses, lipids and hydrophobic proteins adhered to the glass wall. Not only did this reduce the concentration of

these molecules but also the relative relation between them as the adherence was different. I am sure many studies have been performed without ensuring that the spinal fluid was collected in non-adherent tubes and that control samples and controls were handled similarly.

During my many years as a referee in scientific journals and as an editorial board member, for e.g. Journal of Neurochemistry and J Neuroscience Research, the section “materials and research methods” in a paper to be reviewed was regarded as crucial – without quality in selection of material or choice of quality-assured methods the results must be questioned and the discussion therefore of no interest.

In the perspective of research misconduct, which I have been handling as Rector, I would strongly push for a focus on quality in material selection and handling and methods used. Moreover, it is a responsibility of all co-authors when misconduct is found. I have experience of PhD students and postdocs getting involved.

Another example is related to assay quality and quality assurance: The technique for producing monoclonal antibodies, invented in 1975 by molecular biologists César Milstein and Georges Köhler, revolutionized in many ways science and not least in the ganglioside field.

Producing monoclonal antibodies identifying individual molecules was a “hot topic” in the 80s and ELISA technology was used extensively in the field of ganglioside/glycosphingolipid research. My post-doc time I spent in the laboratory of Professor Victor Ginsburg at NIH who was a pioneer in developing silica gel ELISA, separation by silica gel chromatography and thereafter identification with monoclonal antibodies and/or ligands such as cholera toxin.

The most critical part of the work was the specificity of the monoclonal antibodies applied in the assay and many papers were published on their specificity. At the time it was also easy to get funding for these specificity and quality types of studies. In addition you could publish papers showing negative results on specificity. In my view that was completely in line with the critical role of science and resulted in availability of highly specific and high quality monoclonal antibodies for the broader scientific community.

ELISA kits based on monoclonal antibodies became a business with big commercial interest for research and clinical analyses. The positive perspective was the availability of the new tools to all interested scientists and in the clinic. However, early in this process the value of research papers on ligand specificity of the

antibodies declined and was not followed by a responsibility and adequate information from the companies. How many results in the scientific literature might be based on non-quality assured ELISA kits? This concern is most likely transferable also to other technology developments.

Yet another perspective to reflect on is when research focus changes. As I said at the beginning, when ESN started neurochemistry was focused on lipids, “the nervous system being the most lipid-rich organ”. Molecular biology opened new views but was also met by resistance. I remember the discussion on this topic between Professors Svennerholm and Sandhoff, both well known in the field of glycosphingolipids and lipidoses.

The discussion was on the future of molecular biology in general and specifically genetically modified mice in the lipidosis field, Svennerholm being resistant and Sandhoff expressing positive expectations. It was quite an interesting and emotional debate. Looking back, both were right – the models opened the way for mechanistic studies while human material remained crucial for diagnoses and treatment development.

We all know what the future became but the introduction of molecular biology also changed the focus in neurochemistry from lipids to proteins. Lipids, being the result of many enzymes and proteins to be modified, could not easily be applied to this methodology. Hence lipid research declined and I remember, together with other lipid researchers, constantly reminding colleagues that cellular membranes never exist without lipids and lipids are part of metabolic processes etc.

Today, there is a new interest in lipids but for many years I would say that lipid research declined and in particular through less funding and lack of interest from PhD students. This is not the only field where technological development changes funding and development.

Another example with technology focus is electron microscopy. The introduction of fluorescence microscopy opened up for visualization imaging that had not been possible before. At all meetings fluorescence microscopy pictures turned up and at the same time the interest of electron microscopy declined due to less funding and low interest from PhD students. So the technology development in electron microscopy was low as was the number of new generation of researchers in that field. However, fluorescent microscopy could and did not replace electron microscopy and when that eventually became apparent, scientific competence and equipment availability was low.

It is in the interest and the responsibility of researchers to see and promote the necessity of diversity in research questions and technology. We researchers are the ones who review and have impact on research funding from both private and public funders, reviewing scientific papers and deciding topics for scientific conferences.

Coming back to ESN, I will remind us of the background to the formation of ESN. Starting at a meeting in Brussels in 1974, clinical neurochemists expressed the need for a Society of Neurochemistry in Europe. This society should provide a forum for exchanging ideas and new developments in the field and in addition a vehicle for strengthening interactions between clinically oriented and basic neurochemists. This was something that must be considered very insightful and, today, this is often far from reality in the life science field.

Research is often divided into basic and “applied” research and the academic profession strongly defends basic research while the public and private sectors push for applied research – new knowledge transformed into the business or society sector. However, I hope that there is a more general agreement today that there is no border between basic and applied research, both needed but also both need funding. In life science the coupling between researcher within academia and clinicians has been a long tradition. During my scientific career from the time of my PhD studies I have been fostered in an environment of clinical practitioners and researchers.

Interestingly, around the time the Nobel Prize winners are announced and the ceremony is taking place – there are strong voices in the media and from different stakeholders in society for the necessity of basic free research which the winners present. The rest of the year, the voices shifts in favour of applied research. This is obvious not least in medicine.

To be free to choose the scientific questions and methods are key values for universities and their unique contribution to society. However, universities also have a responsibility to society – to openly share new and developed knowledge through research and education but also recognize societal needs of knowledge.

That ESN recognised already in its formation the importance of encouraging and developing contact between basic and clinical researchers must be valued. Neurochemistry is really one example where basic research findings have been applied in the clinic, introducing new diagnostic tools including non-invasive technology to study the brain and its treatments.

The lipidoses were early examples of how clinical and basic researchers together developed diagnostic and treatment tools in the 1950-70s. Another example of the need for co-operation between basic research and the clinic is Alzheimer disease.

Basic research identifying molecular markers for neurodegeneration was transferred to spinal fluid analyses that allowed prediction of the disease and more general ongoing degenerative processes. Without close collaboration between the basic and clinical researcher this would not have been possible. The availability of spinal fluid samples from well diagnosed patients provided by clinical researchers was crucial for the basic scientist to develop a clinically useful diagnostic tool.

Through collaboration between clinicians and basic scientists, clinical questions to be answered by and/or together with basic researchers will be noticed and basic science development will become known by clinicians and developed into clinical practice.

As a young PhD student in my second year, 1975, I was asked by my supervisor Professor Svennerholm to assist at the Swedish conference, preceding the formation of ESN. (The first ESN meeting was in Bath, UK in 1976 and was chaired by Professor Bachelard, who this award lecture is in recognition of). It was an almost unbelievable offer to me as a young and very inexperienced scientist in the field of neurochemistry. All the “big names” were at the same place and in a meeting characterized by openness both socially and scientifically. I was given the opportunity to listen to their presentations and in addition to talk to them individually.

“ESN” meetings (and later also those of ISN) opened my eyes and meant a lot for my increasing research interest. I saw the future and challenges and a research community that welcomed me and was part of my life for more than 30 years. I recognized this when, in 2006, I got appointed as Vice-Chancellor and decided that such a position was not possible to combine with research, with requirements to deliver high quality publications (to get funded) and to take responsibility for PhD students and postdocs, financially and personally.

I spent more than 30 years in science and in neurochemistry, and the Common Thread through the years was glycosphingolipids, starting with method development research for isolation and structural analyses of glycosphingolipids and particularly gangliosides. However, the clinical application varied. My message to you young researchers is that in research you can never foresee the future directions (that is curiosity research) - Professor Schiavo, at this meeting, gave an example where an experimental failure actually opened up new directions.

I never planned to take on leadership in the University – but it happened and I chose to try it.

The scientific career was the fundamental also for the last 20 years as academic institution leader, as head of the neuroscience department, dean for the medical

faculty and finally 11 years as Rector for the University of Gothenburg. Without a scientific background as Professor it is difficult in Sweden to be elected as leader on any academic level – but also management experience is valued and after these years in leadership positions I know that well.

ESN members gave me the trust to be involved in its organisational work. Starting as a Council member in 1992, and as its Treasurer (1994-1996) and subsequently as President (1996-2000). This experience has been of great value, and also an important merit, in my development and career as a University leader.

It is a challenge to take on leadership in academia, including research program leadership and university positions as head of department, dean of faculty and rector/vice-chancellor and continue your own research. The requirement of continuous and frequent publications for funding, the necessity to follow the development in your field through reading, reviewing articles and attending scientific meetings at the same time as you take responsibility in leadership is difficult. However, it is important that university leadership is carried by those with experience in higher education and research.

In my case, and at the time, I managed to continue my research and get funding until I became the Rector. When I was asked to be nominated I realized that this was a fork in the road - either I go back to research 100% or I take on the role as Rector and have to leave the possibility to do research myself. And not only that – it also meant that I would leave the neurochemistry community – not being part of the research collaboration network and not participate in meetings like this. It was a hard decision.

However, as head of the department and dean of the medical faculty I knew that I loved to be involved in the development of research and higher education. Being nominated and elected by the faculty members was a confirmation that my previous work was appreciated. Reflecting – I did leave my research but it still is a part of the development of science but in another position. As Rector, chair of the Swedish Rector conference, member of the European University Association, and now the President for the International Association of Universities, I have carried with me my own research experience in the leadership, policy-making discussions, research funding systems, etc.

I have also been active in promoting better conditions for young researchers, academic autonomy, in development of funding programs etc. The international perspective is as important in leadership as in research projects. The conditions and regulations for research and higher education are so diverse in different parts of the world that I am concerned about knowledge transmission through research and

education to society, and the possibility to reach the sustainable development goals (SDGs) Agenda 2030.

There are some concerns I have met as Rector, which is a take-home message to you all.

The freedom in research and higher education also comes with a responsibility, to always keep quality in what we do. This is expected of all stakeholders in society and we in academia are responsible for that trust. That responsibility is more crucial than ever at a time of “fake news” when facts are questioned and sometimes regarded as unnecessary.

One main concern is the increasing number of misconduct cases in science – I have seen variants such as plagiarism, false data, lack of ethical approval in animal or human studies. The pressure on publications cannot justify lack of quality.

Another concern is the lack of reproducibility of scientific experiments. This is crucial, not least in physics, chemistry, biology etc as well as in medicine. The reproducibility strengthens the hypothesis and results and thus the quality. However, in an article in Nature 2016, an inquiry answered by 1500 scientists, >70% answered that they have been unable to reproduce other researchers experiments, and around one half, also their own experiments. Is it due to the fact that materials and methods are too inadequately described so not possible to reproduce? Is the difficulty to publish negative results a reason to not repeat previous studies?

During my first almost 20 years as a scientist repeated experiments could be published and seen as a strengthening of the hypothesis. You could also publish negative results. The pressure on “numbers and impact” of publications was not high and I believe that gave the researcher time to reproduce their results before publishing and to make quality controls.

Not least I am concerned about the way previous publications are acknowledged. If not in PubMed they do not exist! How many look for publications carried out with high quality but not digitalised. There are findings that were not developed due to lack of technology/methodology at the time. How often do we see references more than 10 years back? How much do we repeat?

Finally

Science is fantastic and I have never regretted my choice to devote my life to science, as a researcher and as an academic leader. To be part of knowledge creation, and dissemination to society, research and higher education is a favour

and I have always loved to go to work. Mondays being the start of another challenging, exciting but unpredictable week. I was privileged by ESN to start my career with excellent neurochemists and a trust that also encouraged me to take on management and leadership in science and Higher Education.

I again send my sincere thanks to the ESN and to all my colleagues that also have become friends over the years.

And to Herman Bachelard who is no longer with us – I still have so much to say.

Thanks for your attention.