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- Editorial -

On the relationship between education and research

Research without education is as impossible as education separated from research. To be able to do research you have to have basic knowledge on the particular subject. The knowledge of today's text books was in many cases fresh research news only ten years ago. It is therefore very important that education has a close connection to the research. Professors, lecturers as well as postgraduate students should all participate in teaching students, since in doing so they also serve as good examples to get students interested in research. The teaching should be a delicate balance between giving thorough basic knowledge and stimulating the students to seek the answers to how something works or how a problem can be solved.

To get an exam at the Faculty of Health Sciences in Linköping, you have to enter deeper into at least one subject and give a report about your work. In some of the programs, for example nursing, the profession is very practical. It can be hard to change these circumstances because the field is not yet prepared to take advantage of the research knowledge that the students possess. It can be hard trying to change a profession from being practical to be based on a more scientific foundation. It is up to the student to use the exam work that he or she has done. Some students are merely doing the research project as a step to get their exam. Others want to share their work with others with the possibility of getting some feed-back. In Linköping we have good oppurtunities to show our research work, for example through this journal or at "The Students Medical National Congress" which is arranged here annually.

A big task for the university is to recruit students to the research education. Interdisciplinary research has become a trademark for Linköping with the "Tema"-research and the research school "Forum Scientum" as examples. A part of the concept interdisciplinary research is to recruit students from a wide range of educational fields so that they can look at a problem from different points of view. To the medical research it is important to recruit students not only from the traditional educations such as medical school and biology but also in an active way finding students from social and healthcare programs as well as from new programs such as medical or technical biology.

It doesn´t matter whether you are a student, teacher or a researcher, everyone has the same goal - to endeavour towards increased knowledge and a greater awareness in society. Consensus, the students' organisation at the Faculty of Health Sciences in Linköping will organize "The Students Medical National Congress" in May. During the spring , the postgraduate students´ section Domfil, will also arrange a research conference, HU Research Symposium, where the postgraduate students will present their latest research to interested scientists, students and the public. We urge everyone to make use of these two great opportunities to get a picture of the research that is going on at the Faculty of Health Sciences in Linköping and to establish new connections.

Wallin L, President of the Student Union
Eklund L, President of the Doctoral Student Section

- Abstract section -

Studies on a Novel Cytosolic/Nuclear Binding Protein for the Eicosanoid 12(S)-Hydroxyeicosatetraenoic Acid

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Hydroxyeicosatetraenoic acids (HETEs) are lipoxygenase metabolites of arachidonic acid. HETEs were long considered to have few or no important biological function - a view that proved to be incorrect. These compounds have now been identified in many different types of cells, and they have been attributed several important actions, the molecular mechanisms of which are largely unclear. This thesis describes the discovery of a putative receptor for 12(S)-hydroxy-5,8,10,14-eicosate-traenoic acid (12(S)-HETE).

Specific high-affinity binding sites for 12(S)-HETE were detected in the cytosol (52%) and the nuclei (18%) of cells of the Lewis lung carcinoma (LLC) line. Similar 12(S)-HETE binding sites were detected in the cytosol of several other kinds of cells and in human platelets. Gel permeation chromatography and density gradient centrifugation indicated an apparent molecular weight of about 650 kDa and a sedimentation coefficient of 20.5 S for the binding sites in the cytosol of LLC cells. Treatment with ATP caused the 650 kDa component to dissociate into subunits. The actual 12(S)-HETE binding subunit was subsequently shown to have a molecular weight of about 50 kDa.

The subcellular distribution of 12(S)-HETE binding sites in LLC cells was found to resemble the distribution of some nuclear receptors of the steroid hormone receptor superfamily. The untrans-formed glucocorticoid receptor has been reported to be located in cytosol in association with heat shock proteins 70 and 90, and Western blot analyses and immunoprecipitation revealed the same two proteins in the cytosolic 650 kDa 12(S)-HETE binding complex.

A possible relationship to the steroid hormone receptor superfamily was also suggested by the observation that the 50 kDa 12(S)-HETE binding protein interacted with steroid receptor coactivator-l (SRC-I), which is known to be recruited to the site of transcriptional activity by several nuclear receptors. The interaction with SRC-1 occupied only when 12(S)-HETE was bound to its 50 kDa binding protein.

In summary, the research presented in this thesis led to the discovery of a novel type of eicosanoid receptor. This binding site resembles the nuclear receptors for steroids and related compounds by virtue of its subcellular distribution, the inclusion of heat shock proteins in its binding complex, and its strictly ligand-dependent interaction with SRC-1.

Human Bone Alkaline Phosphatase Isoforms

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Determination of serum total alkaline phosphatase (ALP) is frequently requested in clinical routine, mostly to estimate skeletal and hepatobiliary status. In this respect, clarification of the various ALP isoenzymes and isoforms contributing to the total ALP activity could be valuable in daily medical decision making. The general aim of this thesis was to investigate methodological, metabolic, and clinical aspects of bone ALP (BALP) isoforms in human bone and mineral metabolism. BALP is a glycoprotein and functions as an ectoenzyme attached to the osteoblast cell membrane by a glycosyl-phosphatidylinositol (GPI) anchor. The precise function of BALP is not known, however, there is evidence that BALP is necessary for initiating bone mineralization.

A weak anion-exchange high-performance liquid chromatography (HPLC) assay was developed for the determination of BALP and liver ALP (LALP) isoforms. Six peaks with ALP activity were separated and quantified in serum from healthy individuals: B/II a minor fraction composed of bone (70%) and intestinal (30%) ALP, and two major BALP isoforms B1 and B2, and three LALP isoforms. Reference intervals were reported for healthy children, adolescents, and adults (range 7-65 years) In healthy adults the BALP isoforms, B/I B1, and B2, contributed to 4, 16, and 37%, respectively, of the total ALP activity. Bone samples were prepared from human femora in order to characterise and investigate the origin of these BALP isoforms found in serum. Cortical bone had about 2-fold higher activities of B1 compared with B2, and trabecular bone had about 2-fold higher activities of B2 compared with B1. Treatment with GPI-specific phospholipase C did not influence the activities or retention times of B1 and B2. Thus, the biochemical differences between B1 and B2 are likely to be due to different glycosylation patterns, rather than the presence of GPI cell membrane anchor fragments.

Decreased B1 activity was observed after 1 week of IGF-I administration, and after 1 month of GH therapy, followed by an increase after 3 months. B2 was not influenced by IGF-I administration, but was similarly increased after 3 months of GH therapy. It was proposed that the initial decrease of B1 could be an effect of endocrine IGF-I action mediated by GH. Different responses of B1 and B2 during IGF-I and during GH therapy suggest different regulations of these BALP isoforms in vivo. Differences of BALP isoforms in metastatic bone disease were found, as well as discrepant effects of clodronate on different skeletal sites indicated by the location of bone pain. Patients with skeletal metastases and healthy males had B2 activities corresponding to 75% and 35% of the total ALP activity, respectively.

Taken together, the BALP isoforms B1 and B2 can be used as early indicators of pharmacological efficacy and, possibly provide information relating to specific bone compartments. Future investigations have to elucidate if they also reflect different stages in osteoblast differentiation during osteogenesis where one isoform is presented before the other during extracellular matrix maturation.

Free Radical Dosimetry employing ESR Spectroscopy for Clinical use. Application to Brachytherapy

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In all radiation therapy treatment it is important to thoroughly determine the absorbed dose in the tumour, in surrounding normal tissue and in risk organs. The dose distributions are usually calculated by means of computerised dose-planning systems. It is however necessary to compare the calculated dose distributions with experimental measurements. For measurements around brachytherapy sources, a tissue equivalent dosimeter material with a wide linear dose range and allowing a high spatial resolution, would be ideal because of the steep dose gradients around brachytherapy sources.

These requirements can be met by free radical dosimetry (FRD), where the stable radiation induced radicals found in some crystalline substances can serve as a measure of the absorbed dose in the substance. The analysis is made by means of electron spin resonance (ESR) spectroscopy. The most common dosimeter material in FRD is the amino acid L-α-alanine.

Various kinds of gel dosimeters are now being developed to obtain a three dimensional dosimeter where the gel is both dosimeter material and phantom material. The gel developed in this work is an alanine/agarose gel, where small alanine crystals are homogeneously distributed in the stiff agarose gel. The linear dose response of the alanine is not affected by the agarose gel, but the signal intensity and the stability of the radicals are somewhat lower because of the wet surroundings. In order to make measurements of the absorbed dose in absolute terms, the gel has been calibrated.

Since a fine spatial resolution is crucial in brachytherapy measurements, a high sensitivity is needed. New dosimeter materials are tested to find a substance with the advantages of alanine but with a higher sensitivity. Here the crystalline substance ammonium tartrate is presented. It is twice as sensitive as alanine, and by deuterating the crystals the sensitivity can be further increased by a factor of 1.6. The dose response is linear at least from 0.5 Gy to 4 kGy, and the energy dependence is even less than for alanine. We thus find ammonium tartrate promising for clinical use.

Cutaneous effects of nerve injury - an experimental study in the rat

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One of the most difficult tasks of the hand surgeon is to reach a satisfactory restoration of the nerve functions of the injuried hand. In spite of the use of meticulous microsurgery, the results of nerve repair are disappointing, particularly with respect to mixed nerve trunks. In order to understand better the factors influencing axon regeneration and to improve further the outcome of surgical nerve repair, experimental studies are imperative. Studies in the rat show that the number of axons crossing a sharp sciatic nerve lesion may be high at nerve trunk level, whereas the sensibility of the foot skin is very deficient. This mismatch led us to study, with immunohistochemistry, the restoration of nerve endings in rat foot skin after various nerve injuries. In addition, some effects of nerve injury on the non-nervous epidermal components are elucidated through histology, autoradiography and immunohistochemistry.

The results show that the occurrence of epidermal protein gene product 9.5 (PGP 9.5) immunoreactive axon profiles in the skin of the foot is statistically normal 3 months after a crush lesion, but deficient 3 months after sciatic neurotomy and suture. The epidermal axon profiles return late after neurotomy and suture. The occurrence of (putative sensory) calcitonin gene-related peptide- and/or substance P-immunoreactive profiles, and (putative sympathetic) tyrosine hydroxylase-immunoreactive axon profiles in rat foot skin is partly abnormal after sciatic nerve crush and very abnormal after sciatic neurotomy and suture, when the contralateral side is also affected

In rats subjected to sciatic neurotomy and suture or neurectomy, the plantar epidermis becomes abnormally thin, but this is not seen after nerve crush. The epidermal thinning concurs with a decreased occurrence of mitotic cells. Both sutured and neurectomized rats, but not crushed cases, showed a markedly abnormal gait. However, rats subjected to selective division of sciatic foot branches exhibited a normal postural and locomotor behavior. In these rats, the occurrence of mitotic epidermal cells was similar on the operated and contralateral sides. This indicates that the effect of sciatic nerve division on the epidermal thickness of rat plantar skin is indirect, probably being caused by an abnormal load situation. The presence of PGP 9.5-immunoreactive epidermal dendritic cells in rat plantar skin is statistically normal 3 months after sciatic crush injury, but significantly increased 1 week-3 months after neurotomy and suture. Finally, we show that the epidermal PGP 9.5immunoreactive dendritic cells present in rat plantar skin represent Ia-immunoreactive Langerhans cells and that the plantar skin of albino rats is devoid of epidermal NKI-immunoreactive melanocytes.

- Science and students -

The Great Adventure

Doing research was a big challenge for me that gave me the opportunity to develop myself and broaden my mind from the strict boundaries in the graduate education system. I was doing my graduate studies in biology at the University of Linköping. After two years I was supposed to complete a minor project with a research team. There I met a stimulating environment where people were active, curious and keen on discussing things. Already from the start I got to take responsibility for my own work and its progress. Meanwhile I felt that I could always ask for advice and talk to my fellow researchers about my project. I also got to discover the sheer joy of discovery when my results contributed new knowledge. After I finished my project I continued to do research in my spare time and once my degree was completed I was determined to start my postgraduate studies, i.e. to pursue a PhD degree. It was a great adventure for me and it still is. To stretch my own limits and continuously learn new things is stimulating. Meeting interesting people from the whole world that I can exchange my experiences and ideas with is truly exciting.

In doing a postgraduate education you also have to teach students. Teaching requires a constant reflection over one's own knowledge so that one can explain it properly and put it in its right context. Only then can the students as well as I genuinely understand the meaning of knowledge. Also I have never felt such a freedom as I do now; freedom in mind and action. Starting a postgraduate education has definitely made me more self-confident so that I have the courage to open my mind to new things and try my own ideas practically.

Besides being a challenge in a positive sense, postgraduate studies involve a certain element of risk. A financial insecurity is common in the beginning of the education, particularly in the medical faculty. Further on, to choose one's supervisor is a delicate matter. This person should act as a mentor in both scientific and personal issues for several years to come. Thus it is of utmost importance to have a good relationship to one's supervisor and great care should be taken to find the right one. Being a researcher takes a lot of patience. To be persistent and endure setbacks is necessary for a successful postgraduate education.

Sometimes it can be demanding to do your research, to teach and simultaneously find time to spend with family and friends. However, I feel that it is not until one challenges oneself and one's limits that a real personal development can take place. One has to dare to take the step out in the unknown and new with an open mind. I hope that many more will take the decision to do a postgraduate education and seize the opportunity to share old and new knowledge and the scientific atmosphere that will encourage new discoveries.

Magnusson A, Postgraduate student