MTC NEWS

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HOW IT WAS DISCOVERED

Astrid Fagraeus: discovery of lymphocyte to plasma cell differentiation for antibody production

Professor Astrid Fagraeus used to say: When the boys were recruited to the army, the girls got their chance (during the 2nd World War). Then she laughed her specific rough laughter, as if she had continued to say: "And I took mine!" She trained herself in pathology. Throughout her scientific career her vision of medical problems was founded in how the organs functioned and looked like. What happened in the organs?, was her question number one.

She carried out her thesis work at the National Bacteriological Laboratory (Statens Bakteriologiska Laboratorium, SBL) during 1944 to 1947. She benefited from the expertise of Drs Jens Bing and Haral Gormsen at the Institute of General Pathology of the Copenhagen University Institute but also the pathologists O Reuterwall and Nils Ringertz in Stockholm with regard to morphological issues.

Astrid Fagraeus defended her thesis in 1948 that

had the title "Antibody production in relation to the development of plasma cells. In vivo and in vitro experiments" which was published as a monograph in Acta Medica Scandinavica.

A connection between plasma cells and antibody production had been put forward by Jens Bing in 1937 and later, as he observed an increased amount of plasma cells in cases with hyperglobulinemia, chronic infections, and myeloma and in tissues such as nasal polyps, rich in plasma cells and antibodies. Others had pointed out the occurrence of hyperglobulinemia in plasmacytoma. Astrid undertook a study to elaborate the significance of plasma cells for antibody production by observing the cytological changes in the spleen.

Thus in 1948, before the model of the DNA double helix, RNA and the link between DNA, towards RNA, towards protein synthesis, Astrid Fagraeus analyzed the relationship between the input of an antigen to that of a new protein formed, the antibodies, with a particular interest in what cells were involved, their localization within the reticuloedothelial system and the lymphoid organs in the body, and the timing of events

.

Her thesis consisted of 8 chapters, or papers if you want, in the form a monograph, which was the form preferred for a thesis at that time. The four first chapters described different control experiments, necessary to prove her point in the later chapters.

She described the weight of the spleen, the lymph nodes, the liver, the bone marrow and the adipose tissues and the content of plasma cells in normal rabbits but also after immunizing with non-immunogenic compounds. She documented the unaltered numbers of plasma cells, the undetectable levels of antibodies in serum to those non-immunogenic compounds, followed by a comparison to the effect of ovalbumin. The latter led to a distinct increase in the number of plasma cells and the level of specific antibodies. She subsequently described the lack of influence on the production of new antibodies and the number of plasma cells by passive immunization and plasmapheresis.

In the following four chapters she described the cytological changes in different organs after a secondary immunization, the gradual development of the plasma cell from the transitional lymphocyte, the immature plasma cell and the plasma cell in relation to the time and peak of antibody response, the distribution of antigens in the organs after intravenous or subcutaneous injection and an *in vitro* model for production of antibodies of spleen (red and white pulp) cells, respectively.

She observed that the change of the transitional lymphocyte, to the immature plasma cell, to the mature plasma cell, occurred in the following order: a diminution of cell volume together with a change of the shape from round to oval after which the nucleus diminished, grew oval, increased in stainability (more basophlic - more ribonucleotides). It assumed an eccentric position in the plasma cell. The nucleoli first increased in the immature cells and then decreased to become inconsiderable in the mature plasma cell, while the cytoplasm successively increased in volume. The number of immature plasma cells were always greater than that of mature plasma cells in the same tissue.

In the *in vitro* model Astrid Fagraeus first documented that the model could in fact be used to study the *in vitro* production of new antibody synthesis. She subsequently showed that the level of antibodies varied with the number of plasma cells *ex vivo* and in particular with the number of immature plasma cells. She also could show that the antibody production primarily occurred in the spleen as compared to that in the other tissues of the reticuloendothelial system, such as the liver, the bone marrow, the thymus and the lymph nodes.

Furthermore, she showed that the stage of development of the cells at the time of initiation of the *in vitro* culture was decisive for the *in vitro* titer of antibodies found in the supernatant. Thus, before the development of the transitional cell (what we now would call B cells) *in vivo*, there was no significant *in vitro* production of antibodies. When the culture contained many transitional cells, the *in vitro* production increased over time. During the time of the most immature

plasma cells *ex vivo*, the *in vitro* production lead to the highest antibody titer, but declined rapidly. With the appearance of mature plasma cells, the titer declined.

Astrid Fagraeus also observed and linked this differentiation process to basophilic structure in the cytoplasm, shown by others to demonstrate the presence of ribonucleic acid. Thus her thesis also described how the differentiation process that resulted in an antibody production was linked to an increase in the cytoplasm of ribonucleic acid. Today we know it, of course, as messenger RNA.

The results suggested, she wrote modestly, that the "formation of antibodies takes place side by side with and during the development of the reticulum cells into plasma cells. In case of an intense antibody formation a differentiation of these cells into plasma cells takes place". She finished: “Thus the mature plasma cell is to be regarded as the final link in a chain of development, a cell that has already passed the stage of its greatest functional intensity.” Or as she used to say with a great laughter: “The plasma cell is a cell that has its future behind!”

When we quoted her that antibodies were produced by plasma cells, she protested and said that it was the cells BEFORE that produced the antibodies. The plasma cell was as close to death as it could be. I doubt that it may be claimed that she discovered the plasma cell, neither that it was the cell to produce antibodies. She gave credit of this to others. What she did in her thesis was to describe in detail the intimate relation of the differentiation process with the cell divisions, the successive roles played of the different cells for antibody production, and how the end cell of differentiation, the plasma cell, was NOT the main actor.

From the first day of my employment in her laboratory in the 1970ies, I felt honored to be in that place. Her grandeur was felt in many ways, such as when I first came to work there. She had given me a bunch of papers to read, but I put them aside and asked if I could continue with my project on measles. She gave me a long look and she protected me and my project, despite that she was not a partner then: “OK, if you publish!”

It has been a great pleasure to have to go further into her thesis, such a milestone in immunology, and in developmental biology as well.

Figure legend:
In the spring we usually had a picnic. Astrid is in the center. Behind her is Reneé Norberg, her deputy, and also Anita Östborn, Karin Winberg, and Katarina Karlén, all still working at the department of Immunology, SMI. I stand in the last row, 3rd from the left, besides Peter Biberfeld.

Anneka Ehrnst

Fagraeuslaboratoriet - SMI's new Experimental Biomedicine Center at KI Campus

In the beginning of 2003 SMI's new Experimental Biomedicine Center on KI Campus will be ready to use. The construction works have already started at "Ryssberget" in the south east part of KI Campus.The Center will be unique in the world because of its considerations of the animals on demand of the Swedish government, which has the strongest rules for experimental biomedicine in the world. For example there will be an outdoor yard for uninfected primates and the cages are the largest in the world.

The Center has a capacity for 150 primates and several smaller animals, mainly rodents. SMI has an extensive international research focused on developing a vaccine for HIV in which primates are necessary, but also non-SMI research groups will have access to the Center.

According to tradition at KI the building must have a name, and after a proposal from Gunilla Källenius at SMI the name will be Fagraeus after Astrid Fagraeus; the eminent female scientist and immunologist at SBL.

Birgitta Brink
Information Officer SMI

COOKING AROUND THE WORLD

RUSSIAN BLINIS

Firstly, I want to express my agreement with a woman who wrote the following.

"... Every housewife in Russia considers herself a specialist when it comes to blinis - a thin, flat pancake akin to blintzes - that are eaten at the end of winter, a period called Maslentisa (pancake week) that coincides with Shrovetide (week mainly the Sunday before Great Lent). The 48 days including Palm Sunday and Holy Week are called the Great Lent, at least for Orthodox. Shrovetide or "Butter Week" occurs in March, the end of wintertime, and blinis simulate the Sun image (in pagan sense).

To be sure, each housewife has her own recipe, i.e., specialty of the house. However, many such housewives do not even suspect that their specialties are only indirectly "related" to genuine Russian blinis.

However, it would be impolite to blame them for that. The multitude of special sorts of flour for frying "fast" blinis, the wide variety of loosening agents, non-stick frying pans, electric ranges and simply the lack of time - all this reduces the cooking of blinis from an art to the level of routine culinary skills.

In Russia perhaps there was only one man who knew the secrets of real blinis that our ancestors ate with relish aeons ago. That man was William Pokhlebkin, an historian and writer, an oddball who sported a long beard and dressed in worn-out clothing, the author of numerous books and cookbooks. The overall edition of his books throughout the world stands at approximately 100 million copies.

So what did Pokhlebkin know about Russian blinis?

Blinis appeared in Russia even before the 9th century, in pagan times. In Pokhlebkin's opinion, the word "blin" stems from the Russian verb "molot" which can be translated into English as "to strike, to thrash, to punch and even to knead" as in "kneading or punching" dough.

Russian blinis stand out by their absolutely peculiar consistency. They are soft, mellow, spongy, fluffy and light, almost semitransparent and with a clearly defined pattern made up of numerous pores. Like a sponge, such blinis absorb melted butter, sour cream and thus become juicy, glossy and scrumptious, Pokhlebkin wrote.

The batter for Russian blinis is mixed 5 to 6 hours before frying them. At first, only part of the flour is dissolved in water or milk together with yeast. After the leavened batter rises, the remaining flour, salt, sugar and butter are added. Sometimes all that is scalded with milk, after which whipped egg whites and cream are added and stirred. After that, the batter must be left to rise again, and only after that, can it go into the frying pan.

Pokhlebkin considers that only small, black iron frying pans should be used for frying Russian blinis. Moreover, such frying pans must never be washed with water. Instead, he recommends cleaning them with warmed vegetable oil and

salt, after which they are to be wiped dry with a soft cloth or paper tissue.

In order to get an even, uniform layer of oil for frying blinis, the oil must not be poured into the pan. Instead, the pan is to be swabbed with oil before each blin. For swabbing, he recommends using a feather, half an onion or a peeled raw potato stuck on the end of a fork.

If the frying pan has been preheated, properly swabbed with cooking oil and has the right amount of batter, the blin will be ready in a jiffy. As soon as it starts rising and acquires a reddish-brown color, its top surface is to be swabbed with oil and flipped over on its backside, otherwise it may become dry. The amount of batter for frying one blin is a matter of experience, Pokhlebkin used to say. But he recommends using a wooden spoon for pouring the batter into the pan.

Pokhlebkin classified Russian blinis according to the sort of flour that goes into the batter: rye, buckwheat, buckwheat-wheat, wheat, millet, semolina and so on.

What the blinis are eaten with also adds to their assortment. It is customary in Russia to eat them with fatty or spicy trimmings by either dunking them into soft butter or sour cream, or wrapping them around salted fish (herring, salmon) and, of course, caviar - black or red, as you wish. In the process of frying the blinis, he also recommends sprinkling the frying pan with chopped onions, diced hard-boiled eggs, cottage cheese and shredded cheese.

He also viewed so-called blin-cakes as one of the varieties of genuine Russian blinis. This is a small stack of blinis one on top of another with different kinds of filling in between them. More often, mincemeat tenderly fried together with chopped onions and diced hard-boiled eggs serves as the filling. He recommends swabbing the outer edges of such stacks with a concoction of beaten eggs, milk and flour so that the filling does not fall out. After that, this work of culinary art is popped into a hot oven for a few minutes..."

My favorite recipe is a simplest one, of course...

1. Milk BLINI (very fast ones)
400 g wheat flour
5 eggs
1ll milk
sugar and salt on the taste
1/3 cup of vegetable oil

Carefully beat eggs, sugar, salt and nearly glass of milk. Add the rest of the milk, flour and beat until smooth. Clarify some butter and use for oiling griddle. Pour about 1/4 cup batter onto lightly greased non-stick fry pan. Bake until puffed and bubbly and light brown. Turn and fry until other side is browned. Only turn once. Do not use too much grease on the griddle. It is also suggested that you skim the batter from the top. Serve with strawberries and sour cream. Place berries and cream in center of pancake and roll up. Or serve with choice of toppings, including caviar, jam, and even thin slices of smoked salmon.

2. Regular BLINI (more traditional)
2- 1/2 cups of wheat flour
1 tablespoon sugar
1/2 teaspoon salt
1 tablespoon oil
1 pkg. dry yeast
1 1/2 cups sour cream (plain yogurt, smetana, gräddfil)
¼ cup of water
3 egg yolks slightly beaten
3 egg whites stiffly beaten

Sprinkle yeast over a ¼ cup of warm water. Stir and allow to proof until bubbly. Blend yogurt with sugar, salt and oil. Stir into yeast mixture. Add flour and beat until smooth. Add beaten egg yolks and beat for several minutes more. Cover bowl and allow to stand in a warm spot for 30 minutes. Stir batter down. Fold in stiffly beaten egg whites. Let stand 10 minutes. Heat a blini pan over medium heat. Pour a scant ¼ cup batter onto lightly greased pan and cook until top is bubbly. Turn over and cook until crisp and browned, about 3 minutes. Hold in a 60'C oven until ready to serve.

Alexei Protopopov

CHAIRMAN´S CORNER

The world after September 11, 2001

Dear MTCers

It is not easy to write this column today. In trying to explain events of 2 weeks ago and the situation in the world to my 9 years old son, I seem to have run out of words. Not that I could find too many to start with. I am not a political writer, and this is not a publication whose editorial should analyze the world situation. So it occurred to me that I should simply leave a blank page, but on second thoughts, I do not think that is a good idea. Because the tragic events and their consequences connect to all of us at MTC, indeed to the whole vision upon which MTC is based.

Some MTCers were in or on their way to the US in the beginning of that week; some have children who live in New York City. All of us travel, we communicate freely with other scientists around the world, we believe in collaboration and learning across the boarders. Our department, with people from so many different nations, working together and communicating with each other, represents the exact opposite of the world that some forces are trying to bring about.

I believe that those of us who are fortunate enough to work in such an environment have a special responsibility today. I can understand if some of you may feel less inspired to work. Some of you may ask yourselves what is the point, what difference will our research and teaching make in a world like this? Some of you may feel uneasy because of comments and tensions that you pick up, within or outside of MTC. Some of you may feel lonely, far away from your families and relatives.

But I beg you to be strong, and take advantage of the privilege that you have: not many buildings in the world offer a more multicultural stage, so many people of different ethnical and religious background – tragically, World Trade Center may have been one of those buildings. We are all here to collaborate and communicate within one set of universal standards, those that are set by science. It is up to institutions like ours to show the world that it can be done, and for a very special cause: to increase the knowledge and the understanding of the world around us and within us, and to provide tools for prevention and treatment of diseases. All of us at MTC, regardless of our specific working tasks, are committed to that cause.

I do not suggest that you should take a casual, ”business as usual” attitude, nor that you should escape by workoholism. But please try to think also of our common cause, and our privilege. Take part in discussions, go to seminars, getting in touch with other groups with interesting methods. Your work is more important than ever! Regardless of your nationality: if you feel uneasy

due to some discussions or comments, if you feel a hostile attitude, do not hesitate to discuss this with your group leader, closest manager or the management of MTC. Be sensitive to these aspects also in your role as undergraduate teacher, in the different courses we are giving today – some students may need extra support. It is our responsibility to maintain and improve a creative, collaborative atmosphere, in the name of free international communication and science.

On Monday September 17th, one of the many cultures represented at MTC celebrated the start of the New Year. According to Judaism we have now entered the year 5762. The common greeting on that day is ”Shana Tova – *Have a Good Year”*. But that was not easy to say this year, and not a suitable title for this column, as originally planned. Still, we have to deal with the coming year, and make it the best possible. Some people say that we live in a different world since September 11 2001. That may be true, but as scientists we already knew that the development of science makes it look different everyday, due to new findings and reports. *We* make it look different, and we can all, in the global scientific community, contribute to the shaping of the world after September 11, 2001.

Klas Kärre

New colleagues in T/A-support!

During summer and early autumn we have had some changes in the T/A support personnel.

Iréne Hemmingson-Klang has replaced Christina Kylander as MTCs Chief Accountant. Iréne has an upper secondary degree as economist, and she has experience as administrator, manager, consultant and finally Head of Economy in numerous small and medium big enterprises. Beside her job, she committed herself to supplementary training in the late 80’s and early 90’s. Then she used evenings, weekends and spare time to study finances and business economics. In 1997 she graduated as “HFU” (“Higher business economical education”). She has also additional competence related to biomedicine, as she is a fully trained nurse and practised in medical care during the 80’s, before she decided to change business. You may find Iréne in room C 368, and her phone number is 6266 (same room and number as Christina Kylander had).

Our new Personnel Administrator is **Eva Pijnenburg**. In June 2001 she graduated from Stockholm University, on a program called “Personnel Administration and Organization”, as Master of Arts in personnel administration. This is Eva’s first job after her examination, but she has ample experience from working life (both in Sweden and Greece!), in running her own small company and personnel (a hairdressing saloon) and as employee. You will find Eva in room C 464, and her phone number is 6732 (same room and number as Carina Tapper had).

In the EA-group (economy-administrative services) we have two administrator vacancies.

Until those positions have been filled, we will have two temporary members of the MTC-staff.

From the recruitment company "Poolia" comes **Zandra Jansson**, and from KI's central economy department comes **Rennie Juwono**. Zandra and Rennie sit in room C 443. Zandra's phone number is 6257, and Rennie's phone number is 7021.

This assistance from Poolia and the economy department is needed until the vacancies as administrators have been filled, which is supposed to happen in October/November 2001.

In the technical support group we also have a new employee, namely **Bertil Lantz**. Bertil, who has replaced Endre Kobold as janitor (while Endre tries out an employment at MEP), is educated as a military officer, but has been working with technical support for KS (the Karolinska Hospital) and a couple of conference companies in Stockholm since the late 70's. Bertil can be found at the reception (MTCs main entrance), and his phone number is 6782.

As substitute for Eva Pettersson (and Margit Saxerholt) in the technical support group is **Håkan Wikland.** Håkan has a background in nursing and at SL (Stor-Stockholms lokaltrafik). Håkan and Bertil know each other since many years, and they are both engaged as officers in the National Home Guard. Håkans phone number is 6782.

I want to welcome all our new colleagues as members of the MTC staff!

Claes Fritsch
Head of Administration

The MTC Social Circle

SUMMER CONGRESS

Summer has passed and the seasons rapidly change again in Sweden. On the whole this year was a good summer despite bits of rain at the beginning and in the end the middle was tremendous. This great weather also coincided with the greatest immunological event to hit Sweden, namely the International Immunology Congress. This meeting was a bit of an MTC affair with our Professor Andrew the Eagle being responsible for the arrangement as well as Robert Harris, formerly of MTC, in charge of entertainment as well as hosting the opening and closing of the conference with his wife. Furthermore, one could not throw a stone and miss a redshirt (conference helper) that was not from MTC.

At the opening ceremony the most entertaining speech was in fact given by Anders Örn when describing the many variants of his name. He had everyone in stitches which was a very difficult task given the number of different cultures present. There was also a prize ceremony for Bill, and his wife, Gates for their donation of money (acquired from all of us suckers who buy from Microsoft) to fight diseases worldwide. Unfortunately Bill was not there, since he could have perhaps helped many people with there PowerPoint presentations. The prize was made by the same woman who has all the sculptures outside the Moderna Muséet. However, Bill was not the only one winning prizes. Our own beloved Prefekt (Klas Kärre for newcomers to MTC) won the Novartis Prize along with some other guys (Moretta, Italy, and Yokoyama, USA) for his work with much loved NK cells and the theory of missing self. Tears of joy and happiness rolled down the faces of the Swedes in the audience as the local boy made good. His acceptance speech was slightly shorter than Julia Roberts' at last year's Oscars but covered his entire work and all those you were involved

from the very beginning to today. Anyway a warm congratulation goes to Klas for yet another award won this year.

Meanwhile, the rest of the conference was spent by most people meeting people that you only meet at conferences. Parties were held all around Stockholm over the whole week. Unfortunately I cannot report on any of these since I do not remember too much from them. So after a week of festivities/work, it all came to an end and our lives went back to normal.

So what else went on over the summer? Due to my inebriated state during the conference my memory brain cells were obliterated so that I cannot remember anything before July. Could someone please remind me!!!!!! Since July nothing social has really happened. Some people have got married, some people have had babies and I guess that some people will be arranging pubs in the near future. So until next time try and be social!

Benedict Chambers

Student Board News

The last Student Board Meeting took place on Wednesday 19th of September. The "bras-room" in the F-house filled up with PhD students hungry for both free sandwiches and for discussions about various important topics. Issues that were covered include:

Decision that Student Board Meetings in the future will be held once every two months

Reports were presented from the different boards at KI and MTC, such as the: Department Council (Institutionsråd) MTC Research Council and the KI Research Council D.F (Doctoral Student Association/Doktorand Föreningen) Information Council (Informationsrådet) Work Environment Committee

Briefly, the most crucial information seems to be that we have a new Student Representative (Doktorandombudsman- DO) at KI, by the name of Jan Torpman (jan.torpman@mf.ki.se) replacing the former DO Nils Mörner. Also noted was that D.F is looking out for new council members, and that ethical approvals are crucial to all dealing with animal experiments and thus will be well worthwhile to check carefully rather sooner than later!

Information was also given about upcoming student activities during the fall:

29/9 15.00-17.00 Seminar with Agnes Wold at the Pharmacol dep. Nanna Svartz väg 2 *"Gender & academic career: Why men and women are still not equal and what to do about it"*

Oct.: Panel debate at KI on *"What is a good thesis"*

Nov.: Seminar with Harriet Wallberg-Henriksson on *"How to write a good application"*

Dec.: Seminar with Swedish Association of Scientist on *"What can the union do for you?"*

Furthermore there was advice given to all those of you soon ready to wrap things up here at MTC and start planning for the Thesis Defense. You are encouraged to contact the Student Secretary Anna Lögdberg, #6263, for instructions needed, or/and have a look at the web on the following url: http://edu.ki.se/research/index_se.html for an extensive guide on how to prepare.

The next Student Board Meeting will be held in November, at which time we will invite Jan Torpman, the new DO to participate if possible.

More later!

Ebba Bråkenhielm

MTC Autumn Kick-off
Thomas Krantz: "Your body language reveals it all!"

Thomas Krantz lecturing

MTC Pub organized by the Department Council for a change

Powerful people showing off

Claes Fritsch busy as bartender

The Russian Corner

Something starting up right here?

Photos taken by Torbjörn Laggar

To be able to enjoy the colors of the photos, please check the pdf file of MTC News at our homepage: http://www.ki.se/mtc/

MTC Papers-of-the-Month

AIDS 2001 Jun 15;15(9):1109-13

Soluble CD23 in cerebrospinal fluid: a marker of AIDS-related non-Hodgkin's lymphoma in the brain.

Bossolasco S, Nilsson A, de Milito A, Lazzarin A, Linde A, Cinque P, Chiodi F.

OBJECTIVE: To examine if measurement of soluble CD23 (sCD23) in cerebrospinal fluid (CSF) is useful in the diagnosis and follow-up of AIDS-related NHL. RESULTS: Significantly higher levels of sCD23 were found in the CSF of the patients with brain lymphoma than in those with systemic NHL ($P < 0.002$) or with cerebral toxoplasmosis, PML and AIDS-related dementia ($P < 0.0001$). The sensitivity and specificity of sCD23 in CSF as a marker for detection of brain NHL were 77% and 94%, respectively. High levels of sCD23 were found in CSF from patients with brain NHL independently of the presence (18 out of 26) or absence (8 out of 26) of EBV DNA. CONCLUSIONS: The sCD23 in CSF of HIV-1-infected patients may represent an additional, non-invasive marker for diagnosis of brain involvement in AIDS-related NHL.

AIDS 2001 May 25;15(8):957-64

Loss of memory (CD27) B lymphocytes in HIV-1 infection.

De Milito A, Morch C, Sonnerborg A, Chiodi F.

We studied the phenotype and the functionality of peripheral memory B cells in HIV-1-infected subjects. RESULTS: The peripheral memory (CD27) B cells were significantly reduced in HIV-1-infected subjects. Ex vivo expression of CD70 (CD27 ligand) on T cells was significantly higher in HIV-1-infected subjects and inversely correlated with the frequency of memory B cells. In spite of the reduced number of memory B cells, in vitro spontaneous and activation-induced IgG secretion was higher in HIV-1-infected patients than in uninfected controls. The hyperactivation status of B lymphocytes in HIV-1-infected patients was further confirmed by the finding of upregulation of Fas and FasL expression on memory B cells. CONCLUSIONS: Memory B lymphocytes are depleted from peripheral blood in HIV-1-infected subjects. Our ex vivo findings suggest that persistent T-cell activation may contribute to loss of memory B cells through upregulation of Fas/FasL on these cells and terminal differentiation into plasma cells .

Gastroenterology 2001 Aug;121(2):310-6

Helicobacter pylori Infection in Swedish School Children: Lack of Evidence of Child-to-Child Transmission Outside the Family.

Tindberg Y, Bengtsson C, Granath F, Blennow M, Nyren O, Granstrom M.

Background & Aims: Helicobacter pylori infection is mainly acquired in early childhood, but the exact routes of transmission remain elusive. To distinguish between risks of intrafamilial and extraneous child-to-child transmission, we studied H. pylori seroprevalence among Swedish school children with varying family backgrounds. Overall, 112 (16%) children were infected. The seroprevalence was 2% among 435 children with Scandinavian parents and 55% among 144 children with origin in high prevalence areas (Middle East and Africa). Conclusions: Our data indicate that intrafamilial transmission is far more important than child-to-child transmission outside the family. The H. pylori prevalence in the parental generation may be a crucial determinant for the child's risk of contracting the infection.

FASEB J 2001 Aug;15(10):1798-800

Suppression of angiogenesis, tumor growth, and wound healing by resveratrol, a natural compound in red wine and grapes.

Brakenhielm E, Cao R, Cao Y.

Resveratrol (3,5,4'-trihydroxystilbene) is a natural compound found in several plants, including grapes, peanuts, and pines, and in their related products. Red wine is probably the most frequently consumed drink that is enriched in resveratrol. We investigated whether drinking resveratrol could suppress angiogenesis, a process of blood vessel growth involved in initiation, development, and progression of many diseases, including cancer, metastasis, and diabetic retinopathy. We found that resveratrol suppresses the growth of new blood vessels in animals. Our findings suggest that ingestion of resveratrol-enriched food could be beneficial for the prevention of cancer.

Proc Natl Acad Sci U S A 2001 Jun 19;98(13):7504-9

The candidate tumor suppressor gene, RASSF1A, from human chromosome 3p21.3 is involved in kidney tumorigenesis.

Dreijerink K, Braga E, Kuzmin I, Geil L, Duh FM, Angeloni D, Zbar B, Lerman MI,

Stanbridge EJ, Minna JD, Protopopov A, Li J, Kashuba V, Klein G, Zabarovsky ER.

Clear cell-type renal cell carcinomas (clear RCC) are characterized almost universally by loss of heterozygosity on chromosome 3p, which usually involves any combination of three regions: 3p25-p26 (harboring the VHL gene), 3p12-p14.2 (containing the FHIT gene), and 3p21-p22, implying inactivation of the resident tumor-suppressor genes (TSGs). In this report, we demonstrate aberrant silencing by hypermethylation of RASSF1A in both VHL-caused clear RCC tumors and clear RCC without VHL inactivation. These data suggest that RASSF1A is the candidate renal TSG gene for the 3p21.3 region.

Circulation 2001 Jul 17;104(3):358-64
Vascular endothelial growth factor-B-deficient mice display an atrial conduction defect.
Aase K, von Euler G, Li X, Ponten A, Thoren P, Cao R, Cao Y, Olofsson B, Gebre-Medhin S, Pekny M, Alitalo K, Betsholtz C, Eriksson U.

BACKGROUND: Vascular endothelial growth factors (VEGFs) and their receptors are essential regulators of vasculogenesis and angiogenesis in both embryos and adults. One of the factors with a still unknown physiological function is VEGF-B, which is expressed in many tissues, including the heart. METHODS AND RESULTS: Mice carrying a targeted deletion in the VEGF-B gene were developed. In VEGF-B(-/-) nimals, no gross abnormalities were observed in organs that normally show high expression of VEGF-B, such as the heart, muscle, and kidney. Analysis of heart function by ECG showed that adult VEGF-B(-/-) mice have an atrial conduction abnormality characterized by a prolonged PQ interval. VEGF- or basic fibroblast growth factor-induced corneal angiogenesis was similar in normal and VEGF-B(-/-) mice. CONCLUSIONS: VEGF-B seems to be required for normal heart function in adult animals but is not required for proper development of the cardiovascular system either during development or for angiogenesis in adults.

Cancer Res 2001 Jul 15;61(14):5441-6
Effects of angiostatin gene transfer on functional properties and in vivo growth of Kaposi's sarcoma cells.
Indraccolo S, Morini M, Gola E, Carrozzino F, Habeler W, Minghelli S, Santi L, Chieco-Bianchi L, Cao Y, Albini A, Noonan DM.

Gene transfer delivery of endogenous angiogenesis inhibitors such as angiostatin would circumvent problems associated with long-term administration of proteins. Kaposi's sarcoma (KS), a highly vascular neoplasm, is an excellent model for studying tumor angiogenesis and antiangiogenic agent efficacy. We investigated the effects of angiostatin gene transfer in in vitro and in vivo models of KS-induced neovascularization and tumor growth. A eukaryotic expression plasmid and a Moloney leukemia virus-based retroviral vector for expression of murine angiostatin were generated harboring the angiostatin cDNA with cleavable leader signals under the control of either the strong cytomegalovirus promoter/enhancer or the Moloney leukemia virus long terminal repeat. Angiostatin secretion was confirmed by radioimmunoprecipitation and Western blot analysis. Supernatants of angiostatin-transfected cells inhibited endothelial cell migration in vitro. Stable gene transfer of the angiostatin cDNA by retroviral vectors in KS-IMM cells resulted in sustained angiostatin expression and delayed tumor growth in nude mice, which was associated with reduced vascularization. These findings suggest that gene therapy with angiostatin might be useful for treatment of KS and possibly other highly angiogenic tumors.

Circulation 2001 Jun 12;103(23):2834-8
Chlamydia pneumoniae infection does not induce or modify atherosclerosis in mice.
Caligiuri G, Rottenberg M, Nicoletti A, Wigzell H, Hansson GK.

Seroepidemiological studies have linked Chlamydia pneumoniae (CP) to coronary heart disease, and recent experimental studies suggest that it may accelerate or even induce atherosclerosis. We therefore evaluated the effect of CP infection on atherosclerosis in atherosclerosis-prone apolipoprotein E-knockout (apoE-KO) and wild-type C57BL/6J mice. CP does not induce atherosclerosis in wild-type mice and does not accelerate atherosclerosis in chow-fed apoE-KO mice. Further studies will be necessary to clarify the explanation for the seroepidemiological association between CP and coronary heart disease in humans.

General News

NEWCOMERS AT MTC

Ida Sofia was born on July 25th to the happy parents Åsa Szekely Björndal and Laszlo Szekely

Staffan Swärd in Mats Wahlgren's group had a son recently who will have the name Johan.

SHORT NEWS

Petter Höglund married Dr Caroline Olgart (Lungkliniken, KS) in the church of Vaxholm on August 25th. . The beautiful bride was wearing her mother's wedding dress and the party was given at Tornvillan by the sea. There was dancing until late in the morning when the newly weds disappeared for their honeymoon in Nice and Corsica. Congratulations from MTC News!

MTC IN THE MEDIA


Insekter nytt vapen mot dödsbakterier

SVENSK PIONJÄR Hans G Boman undersöker en stor peptid med massspektroskopi på Karolinska institutet utanför Stockholm. Massspektrometern bestämmer vikten på proteinmolekyler exakt. Peptiderna skjuts i väg med laser. Ju lättare de är, desto snabbare rör de sig.

Bakterierna finns överallt

Skalbaggar må vara obehagliga att titta på. Men

Så funkar framtidens antibiotika

On August 18th we could see **Hans G Boman** in **Aftonbladet** under "Värt att veta" in a two page article with the title "Insects, a new weapon against deadly bacteria" Researchers aim to replace antibiotics by peptides from the blood of insects to fight the increasing multiresistance,

Hans-Gustaf Ljunggren has been very busy in the media lately: He was interviewed for 18 minutes together with Sanna Cardell in SVT in the program "Bakgrund" about the big Immunology Congress in Stockholm He was also interviewed by the press and radio (DN, SvD, Science Radio, TT etc) regarding Cancerfonden and the Jubilee Conference at Djurönäset.

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Roland Möllby was seen sitting in the TV¤ sofa discussing Microbes in the Atmosphere and **Agneta Richter-Dahlfors** was heard in the Science Radio program. Many MTCers in the spotlight lately!

Marie Bohm

Four new graduate students

Birgitta de Jong: "*The epidemiology of human Salmonella infections in Sweden*." Supervisor: Karl Ekdahl

Camilla Kolmskog: "*Influenza: Antiviral Sensitivity, Receptor Avidity and Prediction of Antigenic Drift* " Supervisor: Annika Linde

Johanna Sigte "*The Role of the 6K Mebrane Protein in Alphavirus Budding*" Supervisor: Peter Liljeström

Eva Bjur "*Macrophage Responses in Relation to Modulation of Bacterial Surface Composition*" Supervisor: Mikael Rhen.

Have you forgotten who is giving a **seminar** today? Check the **new MTC Inner Circle** site and see MTC This Week on **www.ki.se/MTC/intern**

You will find a lot of other interesting and helpful information for MTCers there, blanks, mailing lists, chat possibilities, application deadlines, common equipment, short news. Check it out and you will use it!

APPLICATION TIME

For the October application deadlines, please consult the MTC Inner Circle site: ***mtc.ki.se/intern*** You may also check the KI website: ***intra.ki.se*** by clicking on Forskningsfinansiering/ Funding

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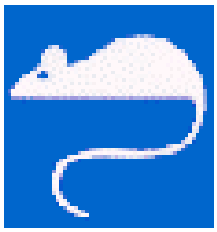

ANIMAL HOUSE NEWS

Dear Friends!

Greetings from the Animal House. I hope your work in our facility is going well and that you are satisfied with us. This autumn will see a burst of new activities. We will soon inaugurate our new P3 facility, in which important questions regarding the *in vivo* effects of tuberculosis infections will be studied in mice. We are excited about the fact that MTC will be able to support this type of research. Later this fall, we will complement the tuberculosis work with that by other research groups who want to perform P3 work in animals.

The P3 work will be conducted in the old "virorisken". All previous activities in this unit will therefore be moved to the reception unit, which for that reason are being rebuilt. We are sorry for the possible inconveniences the reconstruction may have had for you, but hope that within a few weeks we will be up and running as usual again.

As for the reception unit, many of you are aware that there is a waiting list to get your mice in and tested. The reason for this lies partly in the reconstruction, but also in a generally increasing demand for importing mice to MTC. We foresee that this demand will continue to be high, and perhaps even to increase, and we will therefore in this fall evaluate the need for new investments in material and in staff. Hopefully, we will soon be able to increase the capacity in the reception unit and by this offer you a better service.

We have a new veterinarian at KI with a special responsibility for our animal facility. Her name is Anne Waldemarsson. Together with her, we are planning improved routines in many areas of our animal house. Please feel free to contact Anne

directly as well if you have questions regarding your mice. I am also consulting Anne with regard to the ethical applications you write and for which you need my signature. This is a good thing because it helps us avoid pitfalls that could delay decision in the ethical committee. We will of course try to comment as soon as possible, but please come to me for comments and a signature in good time before you need to submit. If you have still not given a copy of your valid ethical permissions to Maggan, please do so.

That's all for now! Hope to see you all every now and then passing by my room for a chat!

Petter Höglund
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petter.hoglund@mtc.ki.se

WHAT OLD BONES CAN TELL

Skeletons In Our Closet: Revealing the Past Through Bioarcheology
From a book review in Nature, August 2000, **C S Larsen**, Princeton Univerisity Press.

We think of the agricultural revolution as an unqualified benefit to our species, but Larsen demonstrates that it is also had substantial negative aspects. Overall health was reduced by the introduction of agriculture.

The native peoples of North America have survived two traumatic events during the past two millennia. One we all know about, the arrival of the Europeans with their freight of diseases and their ability to destroy whole ways of life almost overnight.

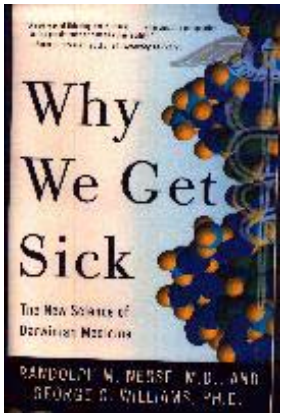
The other, earlier event is less obvious: the transition from a foraging way of life to one based on grains, which happened more recently in North America than the agricultural revolutions in other parts of the world. Both events left many traces on the skeletons of the people who lived through them.

Larsen and his collaborators have examined burial sites in Stillwater Marsh, Nevada covering the time from 1300 BC to AD 1300. Isotopic analysis shows that the people living there ate plants gathered from the marsh and animals that they hunted. They were strong and healthy, with few signs of vitamin deficiency and virtually no tooth decay. Nonetheless, their teeth show signs of periodic famines.

The story was very different with pre-Columbian people living on St. Catherine's Island, Georgia. Skeletons dated from 400 BC to AD 1450 show a transition to ever-higher proportions of corn in the diet, accompanied by a huge increase in tooth decay and changes in the bones that indicated a more sedentary life. Jaws became smaller with the introduction of corn mush into the diet, and teeth were more crowded. The teeth were slightly reduced in size during this period. Famine was less common than at Stillwater, but in spite of their more reliable food supply there is little evidence that these people lived any longer than those in Nevada.

Read by Eva Klein

Illustrations are not taken from the article.



Why we get sick -

a review abort a book that is worth while

I have during the long Swedish summer nights come much to enjoy a book that was recommended to me by Richard Dawkins upon his visit last year to KI (well, um, ok not all that personal communication, rather it was mentioned for all to hear at the Nobel seminar). Anyway, when an advice is given by an Authority in such enthusiastic manner one (as a mere graduate student) must but follow!

Why we get sick is written by two American professors: one (Randolph Nesse) a practizing physician, the other (George Williams) an ecologist and evolutionist. Their book deals with an evolutionary approach to understanding human illnesses & ailments such as pregnancy-related morning sickness, obesity and the sugar drive, what pain is good for, how bacterial arms race against antibiotics should be viewed and why we humans, unlike an injured lizard, cannot regenerate a lost limb. There are also ample thoughts on why we will never be able to live forever and why myopia probably never really posed a problem for people living in the Stone Ages.

To be completely honest, I have yet to finish the book, but rather I find myself dwelling delighted on each chapter. At the moment I am contemplating the Diseases of Civilization, such as for instance the fact that a large proportion of today's children suffer so many problems with their teeth. The authors blame our deficient use of jaw muscles in the early years of life for " *their underdevelopment and indirectly weaker and smaller associated bone structures"* as the cause for malfunctional positioning of the teeth. Their resolution to this problem? Unless you can convince your kids to start chewing seriously on woods or plants, let prolonged vigorous biting be considered a prestigious athletic attainment for children and thus put chewing gum on the school schedule!!

As also a significant part of my summer holidays were spent in and out of lovely pubs in Dublin, I feel most urged to include a thoughtful remark taken from an old Irish ballad quoted by the authors of **Why we get sick** in a chapter about "Aging as the fountain of youth":

Let's not have a sniffle,
Let's have a bloody good cry.
And always remember the longer you live,
The sooner you'll bloody well die!

Ebba Bråkenhielm

STUDENT LIFE
Postcard from Würzburg

This summer I visited a German lab, a university hospital laboratory in Würzburg, Bavaria. This was a small lab with an all-German staff, so I thought this would be a good place to get a sense of the German spirit.

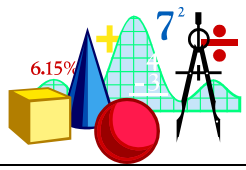
Würzburg is a beautiful town about the size of Uppsala. It is situated in the Main valley, with the river running through the city. There are two main things to see here. One is the flashy residence, built by one of Würzburg's many prince bishops, known today mainly for building the residence. The other is a big fortress up on a steep hill. Nobody ever captured it except the clever Swedes, who bribed their way in during the Thirty Years' War, and subsequently brought the prince bishop's valuable library to Uppsala. If you manage to get hold of a 50 mark bill before they disappear, you can study engravings of both. Also, highly successful research has been done here in the past, as it was in Würzburg that Röntgen discovered the X-rays.

Röntgen's old lab pointed out by a Würzburger

Everybody in the lab staff had either a medical or a laboratory technician background. The lab was well equipped, but lacked more expensive equipment since there were no core facilities. The structure of the buildings was not open like MTC, and over all there seemed to be very little interaction between the labs, and few seminars. There was quite a bit of routine lab work going on, patients came and went, and the doctors had to run off to an operation every now and then. But at the same time, research was done, in part by medical students doing their Doktorarbeit, which is like a one-year "examensarbete".

I was pleasantly surprised by the good atmosphere in the lab, it was not as strict as I had feared. For instance, you only had to say 'Sie' to the professor. People seemed to have a good time, and for instance they cooked together every once in a while. It seems like the differences compared to MTC depend mainly on it being in a hospital, and not so much that it is in another country. I guess this lab was not unlike some labs on the other side of Solnavägen.

Stefan Termén



Research-Group-of-the-Month

THE MIKAEL RHEN GROUP

Starting from the youngest member, the group includes **Noak**, the lab-pet. Ranked by age, Noak is followed by the graduate students **Eva Bjur, Sofia Eriksson** and **Dilek Tezcan-Merdol.** Then we have the ones not gaining age anymore, which includes myself and **Marianne Ljungström** affiliated to the group through SMI.

As a research group, our activity is focused on two main issues: i) how pathogens replicate within a host, and how an infection spreads. To answer such questions we apply two different model systems, the first being based on *Salmonella enterica* and its infection pathogenesis. Serovariant Typhimurium of *S. enterica* is a well-characterized bacterium which has served as a laboratory model organism for studying basic biochemistry and genetics for decades. The same bacterium is also a pathogen for both man and animals with the ability to cause a severe systemic disease, for example, in mice. Mouse virulence is strongly correlated with the bacterium´s ability to grow inside phagocytic cells, and bacterial mutants devoid of this capacity tend to be avirulent. This set-up makes Typhimurium a perfect tool for probing details of

pathogen-phagocyte interactions. Also, *Salmonellae* are capable of establishing chronic infections both in man and animals, which provides an interesting platform for studying persistent carrier states.

The other model organism we are working on is *Campylobacter*. *C. jejuni* is the most prevalent domestic bacterial agent for gastroenteritis in Sweden. The problem is that besides from unpasteurized milk and contaminated water, we do not have a conclusive picture from where we actually get the infection. Furthermore, the bacterial genes participating in the infection pathogenesis are not well characterized. Therefore, we are trying to trace the route of infections using molecular typing approaches, and to define virulence characteristics in *Campylobacter* that could function as trademarks for human-associated strains and disease.

While this all may sound confusing, we have tried to specify the matter by stipulating specific tasks for each member of the group.

Eva Bjur. Eva's task is to study how a phagocytic cell recognizes the *Salmonellae* in the first place, and how such recognition is converted into different host activation responses. The background to this questioning arises from our observations showing that bacterial mutants with altered surface structures are treated differently in terms of being exposed to phagocyte innate defence responses. The hypothesis to be tested would state that different surface structures would be associated with different combinations of host cell receptor usage upon recognition and uptake of the pathogen, resulting in different concomitant events.

Furthermore, while *C. jejuni* may cause a rather unpleasant gastroenteritis in man, the same bacteria can be kept as asymptomatic commensals in birds. Thus, one could ask whether this divided infection picture could emerge from some hosts being more prone to induce an inflammatory response to *Campylobacter* than others, and again, if this is associated with differences in the use of phagocyte surface, complement or scavenger receptors.

Sofia Eriksson. Sofia's questions are closely associated to those of Eva, in that Sofia studies how the bacteria can withstand host innate defence effector substances, such as reactive oxygen and nitrogen compounds. Sofia defines the bacterial response strategy as being divided in a defensive and an offensive arm. The defensive arm protects the bacteria from the reactive compounds. In parallel, it includes damage control systems for repairing the injury that still occur in the bacterial cell. The offensive arm is connected to bacterial manipulation of host cell receptor usage, concomitant signal transduction pathways and intracellular vesicle maturation. For example, Sofia is defining mutants of sv Typhimurium having the capacity to prevent NO production from inducible nitric oxide synthase. Such an inhibition could be achieved by depriving iNOS from one of its essential substrates, L-arginine. This again could be achieved by alternative activation of the host cell leading to omitted induction of arginine transporters, or in the induction of arginases.

Dilek-Tezcan-Merdol. Dilek's main task is to define how *Salmonellae* induce intracellular replication using their *spv* virulence genes. The expression of these bacterial genes inside the phagocytic vacuole leads to release of the SpvB protein, which in turn ADP-ribosylates the host cell actin. This modification will prevent the conversion of G actin into F actin. Thus, Dilek's two main questions are how, in molecular details, the bacterium can sense the intracellular environment for the activation of *spv* gene expression, and how the subsequent Spv-mediated modification of host cell actin is connected to bacterial intracellular multiplication. For the moment though, Dilek appears more occupied with her own rather than with salmonella´s replication.

Marianne Ljungström acts as our backbone when it comes to the identification and typing of *Campylobacter* isolates. For this, we have applied and developed new techniques allowing us to identify, type and subtype the various isolates. The interesting problem here is to define a consensus for typing criteria; *Campylobacter,* much like *Helicobacter pylori,* turns out to be highly variable in terms of DNA alterations. Thus, we have to define the origin of these

alterations before we can assess the validity of any of the methods for subtyping. The immediate spin-off from this project is that we will get a representative collection of domestic *C. jejuni* isolates, each with its defined epidemiological origin. Such strains can e g be used by Eva Bjur for studying differential innate responses to *Campylobacter*.

The role left for the younger of the oldest is to carry out anything the others do not bother with. Besides preparing buffer, growth media etc, I am trying to tie up the observations made by others into nice stories. For one thing, together with **Mark Clements**, the former post-doc in the lab, and Professor **Staffan Normark**, we have identified a regulatory mutation which governs the transition between acute versus chronic infection states in sv Typhimurium. The bacterial regulatory factor is polynucleotide phosphorylase which regulates the expression of bacterial adhesion to eukaryotic cells, invasion functions and the expression of *spv* genes. Thus, many of the separate lines seem to end up at the same point, defining a connection between adaptation to phagocyte milieu, bacterial intracellular growth, persistency and virulence.

Finally, each and every one of us is involved in collaborations with other labs within or outside MTC. At the moment the most active external collaborators include Professor **Friedrich Koch-Nolte** from Hamburg University Hospital through his input in our *spv* project, and **Karin Valegård** from Uppsala University through a project resolving the structure-function relationship of a bacterial gene thermoregulator protein TlpA.

What about the youngest then? Well, **Noak**´s mission is to be social and constructive; he listens well, does not argue and we assume he acts as a constant source for obscure variants of *Salmonellae*.

Mikael Rhen

MTC SPORTS CLUB

Hello Everybody,

Hope you have had a nice summer. I certainly had, a looong stay in my paradise, the isolated island Skabbholm in Åland. See separate article!

During this period a lot of MTCers have represented the department in several different ways: Rose-Marie Lövenstig and Birgitta Wester have participated in the "Tjejtrampet", a bicycle competition for women, Birgitta also ran "Tjejmilen". A lot of girls ran in the "Vårruset", please forgive me but I don't have all the names, and some of us, Anita Wallentin, Birgitta Wester, Rose-Marie Lövenstig, Erika Assarsson, Anna Aleman and myself, participated in the Olympic Day Run, a competition run in 65 countries around the world. It is a 6,7 km long run around Riddarfjärden in Stockholm in the sunset. And best of all... You don't have to run, you can walk if you want, **"***The most important is to participate, not to win***!!"**

But, WHERE ARE ALL THE MEN??? I'm sure you are out there doing a lot of sports.

I would like to know if there is any interest in organizing a day out in the forest now during the autumn? We have the Tyresta National Park close to Stockholm and some parts are easy to get to by bus and also to get home.

Now during September and October KI has an activity program called "Keep your heart going" and you should fill in a form every time you do some physical activity for more than 30 min. and when it is full you send it in to Yvonne Kahlin at

Stallet and you have entered in a lottery. It is part of the "Keep Sweden Going 2001"!

The Bellman and the Lidingö relays are next on the program for the running team and we wish that some of you would like to come and cheer for us. The Lidingö relay is on the 5th of October at 3 pm. I will put up a reminder!!!

See you! If you want any information, don't hesitate to contact me!

Mia Löwbeer
C357, ext 6203, 6772
Mia.Lowbeer@mtc.ki.se

AII launches a new undergraduate course to strengthen the clinical connection

The KI research education program AII (allergy, immunology and inflammation) is one of three PhD programs at KI that has its administrative base at MTC. We hope that AII will provide a common ground for all PhD students at KI engaged in AII research in the future. We who run AII on a day-by-day basis are myself, chairman of the steering committee, Louise Berg, our study administrator and Anna Lögdberg, who is presently designing our coming web page.

One of the main tasks of AII is to coordinate PhD courses. They are given all over KI, including MTC. Examples of MTC courses within AII are one on the Intestinal Flora by Roland Möllby and Lissa Norin and one in Molecular Immunology given by Klas Kärre and myself (coming this December to a lecture hall near you). On a hopefully expanding list, we currently have 17 courses on our program.

However, at the moment we are especially excited about another aspect of our program – a new research preparatory course that we hope will help to build bridges between preclinical and clinical activities as well as to facilitate recruitment of talented PhD students.

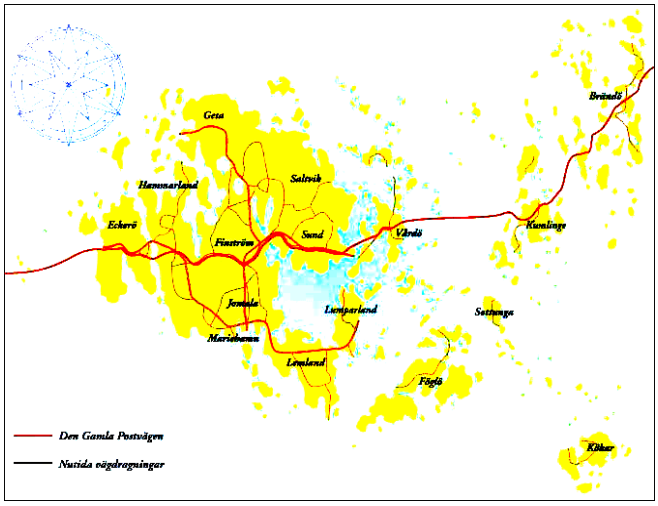
During this 20 p course, each student will conduct an extensive project within a preclinical research group that has an AII orientation. This work is complemented with two placements of a week each at two hospital clinics. The idea is for students to meet patients with diseases that are of relevance to their projects, attend different treatments and investigations and thus gain insights into clinical work and research. Possible clinics include those specializing in allergy, rheumatology, neurology or endocrinology, and the idea is to find a close match between the student's project and the clinical reality benefitting from it.

Students from relevant university programs in Sweden and abroad constitute the main target for our recruitment efforts. Those students today make up a large part of PhD students within AII. However, also medical students can benefit from direct patient contacts early in their research career. During the course the student are eligible for a student loan, but the supervisor also has the possibility to offer a scholarship.

Students and supervisors interested in the course are encouraged to together submit an application to the steering board of AII. Application for can be found here (link). Students will be continuously admitted to the course so there will be several application deadlines throughout the year. First application deadline was September 17, but there will soon be another one!

Take this opportunity to try potential students out, in a way that gives them a taste of what preclinical medical research is all about in the end – helping and curing patients!

Petter Höglund
Chairman AII steering committee
728 62 01 petter.hoglund@mtc.ki.se



My paradise!!

(So beautifully described my friend Susan Patterson, USA, who visited me, Mia Löwbeer, in my paradise in Åland, Finland, in May 2001.)

Imagine summer vacation on an island populated only by yourself and your dogs. There will never be total darkness, mail delivery or electricity. No motor vehicles, roads or running water. Your camp consists of a modest cottage, bunkhouse, and out buildings which perch just inside the tree line atop a rock outcropping on the island's windward side. You cook on a propane stove, a grill, or over an open fire. Fresh fish are an easy catch just steps from your front door – salmon, pike and ocean perch of a size that draws eager anglers from around the globe.

You and the dogs can walk, hop, hike, climb and jog your way around the island in under an hour. The windward terrain is wind-scoured rock that used to be beneath a Scandinavian sea. Approximately two additional inches of shoreline is revealed each year by the receding waters. Upland, lichen lines crevasses, then spread into carpets that lead the way to element-dwarfed and stunted shrubbery. It is only as the curve of land attains the protection of the leeward side that you can immerse yourselves in the lush growth and cathedral-like environs of the forest-roofed and wild blueberry floored summer shade and silence.

Watch your step! The thick undergrowth disguises the uneven footing, and the scenery distracts your attention from what might trip you. The dogs leap and cavort like fawns over fallen limbs. They gamely scramble atop boulders, 'king of the hill' gleaming in victorious eyes, and dripping from dangling tongues. You, however, might twist an ankle if you're not careful!

The dogs lead you in the familiar trek back to "civilization". Thirsty tongues lap up the surprisingly fresh water at the shoreline while you quaff with Koff, kept cold in a propane-powered little 'fridge'. Yes – fresh water offshore! The rainwater that percolates through the ground of this island and others like it, seeps around and ends up as part of a fresh water 'cushion', so to speak, of fresh water. The entire archipelago of which your little island is one of 6500, is a mixture of fresh, blending into brackish, blending into the salt of seawater. The area marine life has likewise adapted to its unique environment.

All this talk of water – and the sight of which fills your vistas – reminds one that 'what goes in, must come out'! Ye Olde Outhouse awaits the anxious and over-filled an easy walk down a well-worn path back of the cottage. Not surprisingly, it is in the center of a web of converging paths. If your legs don't quite measure up, you'll have to master the hop up to the high, wide seat. A generous side window allows plenty of light – and a great view – by which to peruse a handily stacked collection of publications - if you read Swedish!

Supply runs are accomplished via a modest motor launch across the bay to the neighboring main island of Vårdo, "home of sea captains and authors" (according to the tourist literature). No argument here – your cottage was built by a sea captain for his family's simple getaways, and his daughter is your hostess!

Pull the boat safely up on the rocks and mind your don't step on cow patties as you cross the field to the shaded lane where the cars are parked. If it's not too hot, the dogs accompany the supply run, their crates kept in the back of the car. You head to the village to check your email at the library, do banking and buy the week's supplies. Some days you might go to an exercise class (human company!), visit relatives still living on the island, or take a dog to one of the island's dog club's training classes. Oh yes – dog people even here have themselves organized!

If your launch is too fully loaded with either supplies or visitors, your trip across the bay will be a wet one, 'gunwales to the water'! Hope for sun and snappy sea breezes upon landfall for drying the dampened…whatever!

The dogs are having the time of their lives – they have the run of this place, and being surrounded by the sea, there is no need for any other restrictive barrier. The older dogs teach the youngsters about the particular doggy routes going everywhere and anywhere, and about eating the wild blueberries come July.

No need for water bowls when all the refreshment needed is within easy reach of the dogs. They also have learned, as perpetual sun gradually warms the water, that swimming with the humans in the cool, clear clean bay is fun. Occasionally, a cow from the farm across one end of the island will wade/swim through the growing marsh being formed as the waters recede. Driving bovine invaders back whence they came is terribly exciting, and a vital part of the island security detail to which the dogs naturally assign themselves.

The islands have several flocks of swans, and the dogs watch with respectful interest as the beautiful birds mate, nest and then parade their cygnets past the shore on their island tours. The pair of nearby sea eagles are a treasured sight – themselves as big or bigger than the dogs… The eagles mix freely with the swans on Vårdo's seaside meadows, looking for all the world like bouncers at the Bolshoy.

The cool night air is warned temporarily by the little wood stove in the cottage living room. There are so many deadfall sticks underfoot that fuel is always at hand. At night, so many little "senji" bodies under the covers will keep anyone warm. After a good meal and completion of clean up chores, snuggle time is a welcome end to another island day. Despite the lack of a nightfall, a day full of sun and sea air leads inevitably to sleep. Another day in paradise will start – once again! – soon enough.

…. The previous account was inspired by a visit to the Karlsson family island where Mia Löwbeer and the Yulara basenjis were excellent hosts and guides to some recent American visitors (who continually wished for a way to share the magic of the experience with their own basenjis!).

Sigh. Åland living in the archipelago's islands is so awesome, I even had to name a part-Finnish pup after the place. There are no palm trees, no glitz, no glamour. Pastoral countryside, stepping-stone islands, islets and skerries – it's not a tropical venue. The interests here are fabulous fishing grounds, incomparable birding opportunities, fun festivals, Åland dark bread (4 days in the making!), and sailing, swimming and never-setting Scandinavian sun. A 7:1 exchange rate in the dollar's favor makes this a steal of a getaway for Americans. Must return! And you should treat yourself to a visit – there are plenty of reasons that Swedes and Finns call Åland 'paradise'!

Susan Patterson
North Carolina, USA

DET LILLA

innehåller ofta det stora.

Tänk bara på de frön vi sätter i trädgårdslandet på våren. Dessa till synes oansenliga kan växa upp till imponerande solrosor.

Underskatta aldrig det lilla – det kan vara fröet till något stort!

Ur "Grunnaren I"
Av Gunnel & Kjell Swärd

WEBMASTER'S LATEST

There are a few items that could be of interest in this issue of MTC News. One is that we are now officially releasing the MTC intranet and we really want some feed back on the functionality of: http://mtc.ki.se/intern/. Just remember one thing, if you want to post something on the bulletin board you have to ***register*** *first at http://mtc.ki.se/intern/zorum/.*

Another thing that might be of interest is the MTC Staff database. You can check that the information is correct for yourself or for your group by visiting
http://www.mtc.ki.se/staff/index.htm
and do a search with the appropriate key words.

For those that experience difficulties in connecting to the web-server can visit these pages or otherwise contact me
http://www.mtc.ki.se/misc/protocol_pc.htm,
http://www.mtc.ki.se/misc/protocol_mac_at.htm

That's all for now folks

Per Hagblom
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NEWS ABOUT THE POSTGRADUATE PROGRAM IN TUMOR BIOLOGY & ONCOLOGY

This postgraduate (forskarutbildning) program within the KI is funded by the Board of Research Training as a result of an initiative from the Cancer Network of the KI.

The following departments have formed the program: Microbiology, Pathology & Immunology (IMPI), HS; Oncology & Pathology, KS; Medical Epidemiology (MEP), KI; Center for Molecular Biology (CMB), KI; Microbiology & Tumor Biology Center (MTC), KI and Biosciences, Novum, HS.

The scientific- and program coordinators respectively are Ingemar Ernberg and Anna Lögdberg.

Within the program will be provided some 5-10 courses/year: one introductory course annually (2-4 p), and different specialized courses (1-4p), which are given once every 2-4 years. The program courses are open to all postgraduate students (within or outside KI), but particularly designed to serve students in tumor biology, oncology and adjacent fields.

There will be an information meeting held on **November 14th 14.00-16.00** at KI **(Lecture Hall Bertil**, Berzeliusväg 3) where the supervisors and graduate students in the tumor biology & oncology fields will be invited to learn more about the contents & plans for the future of this program.

For more detailed information please have a look at the program homepage at: http://mtc.ki.se/education/tumonc/

Ebba Bråkenhielm

RECIPES FOR THE STUDENT ECONOMY

The MTC News has been giving us recipes from different parts of the world, which has filled some of our kitchen with exotic fragrances, this is what fills the rest of them. I give you some easy recipes for the student economy, and they are fast to make which is important to the student nature.

Noodles
Usually produced and packed in Asia. Never buy the packages at ICA as they charge you 6 kr per package., The cheapest noodles are the ones you buy at small Asian markets. If you want to add some extra taste to the meal I recommend Sweet Chilli, buy a bottle for 14 kronor at the Asian market while you are there. Take the noodles out of the package and boil for 3 minutes, serve.

Macaronis with ketchup and peppar
I once made new friends at Hultsfred Festival with this ancient student meal. Take macaronis and boil them in water with a pinch of salt. Don't boil them longer than the producer suggest on the package, you don't want to lose that al dente feeling.
Add ketchup (cheapest at Prisextra) and peppar, you can always get small easy-to-serve-bags from McDonalds. Serve and enjoy!

The green stuff
We all know the benefit of a piece of broccoli once and a while. Go to Hötorget late in the afternoon and haggle with the sellers. Walk around, different stands have different prices so don't buy all your vegetables at the same place.
The good thing about vegetables is that you don't always have to cook them, you can have them raw. Use your imagination and add some to your noodles or macaronis.

Dessert
Candy in different forms.Gott o Blandat is often sold at low prices, especially on Fridays. Plockgodis is always a good alternative, but don't hesitate to walk that extra mile between different stores. Prices are constantly fluctuating and if you are paying 7 kr or more per hekto you are being ripped off.

Drink
Beer, somehow the average student always has money left for alcohol. If you're low on cash I highly recommend the MTC Pub. I also urge you to take the course about Laboratory fermentation techniques for domesticated microbes, read between the lines in the course catalogue.

Anna Berg

Science and Terror

On the morning of the "Black Tuesday" September 11 I was participating in the 2001 International Annual Meeting at the Institute of Human Virology, Baltimore, USA, Stanley Prusiner had just reviewed all the recent developments on prions and mad cow disease, when at 09.45 we were told by the chairperson that an airplane had flied into the World Trade Center and there were rumors that a smaller airplane had hit the Pentagon. Surrealistic, unreal feelings. Rumors. Unbelievable. You all know the rest.

Baltimore lies on the string-of-pearl major east coast cities, Washington, Baltimore, Philadelphia, New York and Boston, from south to north. Less than an hour from Washington, DC and some two hours from New York. So we followed the events from the first line, fortunately without getting really involved. Several MTCers and former MTCers were at the same meeting. Britta Wahren had left the evening before. In the end I was stranded for four extra days in the US due to the air traffic breakdown.

The hotel where the meeting was held lies in the inner harbor of Baltimore, a very modernized and touristic transition from the old, dirty industrial and shipyard harbor that was torn down some 20 years ago. It is a nice place, basically, just a km inward from Fort McHenry that is the only American historic "shrine" as it defended Baltimore against the British in their last attempt to recapture control of the United States. The successful defense on September 14, 1814 discouraged the British from their continued effort and they gave up the effort. This day gave birth to the use of the American Flag as a fully accepted national symbol and also the National Hymn "The Star-spangled banner" was written during the day of the battle by one observer, Francis Key Scott. By the transition of Baltimore's harbor it is now, normally marketed as the "charm city".

Within hours charm city together with rest of US closed down. The meeting and hotel was localized 300 m from the only small skyscraper in the region, the World Trade Center of Baltimore. It was surrounded by big trucks with loads of sand (to block any potential suicide bombers with cars), by loads of policemen and all boat traffic in the harbor was also closed down.

This was the environment we lived in for 3-4 days. Paradoxically a wonderful weather with 25-30°C and cloudless sky during the whole time. Those at home followed the events as closely as we did, but we also saw all the time the everyday life that tried to go on in the country. And the follow ups there were of course even more intense. No other news penetrated through the news channels for the first 4-5 days.

The excellent scientific meeting went on until Thursday 13th, undisrupted apart from silent minutes for the victims. The last day was cut down because the majority of the invited American speakers had left or could not make it because of air traffic close down. But Science was something we stuck to and which kept our minds a little bit busy, while the unconscious tried to handle the unspeakable, the horror and all the crossing and confusing feelings inside. The American media (CNN, ABC…), the American public, the mayor of New York, Giuliani and the President on site behaved in a very impressive way! It is unimaginable to us what a trauma this was and is for the people of a freedom loving nation. I am still without words in face of the personal tragedies.

Ingemar Ernberg

Remembering the victims of the terrorist attacks in the USA