



ECFS Newsletter

Issue 22 April 2007

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Letter from the President

Dear Friends

The spring light has finally come to Sweden. I am in bed due to myocarditis after a bad influenza virus. I am supposed to lay here and do nothing and you may realize that I do have a hard time with this. Meanwhile my vice president Stuart Elborn and other Board members will do some of my travels that were planned this spring.

Our ECFS consensus meeting on genetic testing took place at Garda, Italy last week. Carlo Castellani, our ECFS secretary from Verona, was in charge of this meeting. It has actually been easier than we thought to get sponsors, which is encouraging. It is good to know that the pharmaceutical companies invest money for longer projects. We hope to be able to follow next with a European consensus meeting on neonatal screening.

Kris de Boeck from Leuven, Belgium, will participate in the yearly American TDN meeting and will give a report during this meeting on how far we have come in our planning for our European CF Clinical Trial Network (ECTN). The Americans are very supportive. We do not want to mimic the TDN but we can learn from their experience; Kris will give a report in the next ECFS newsletter on how this work is progressing.

In April we also have the basic science meeting coming up in Portugal with Margarida Amaral and Ray Frizzell from USA co-chairing this year. As always the program looks interesting and intense. Please take a look at our webpage.

Then we have our 30th ECFS conference in Belek, Turkey. I think we have succeeded in getting a well balanced program for our mixed group of participants.

Once again visit our webpage if you have not already decided to go. I think you will find it

Contact Information

Please e-mail

info@ecfsoc.org

or fax

+45 8667 6290

or write to

**European CF Society
Kastanieparken 7
7470 Karup
Denmark**

interesting and hopefully the program will convince you to come to this beautiful country where west meets east.

I also would like to mention our first European young scientist meeting that ECFS is holding in collaboration with the CF patient organisations in France, Germany, Netherlands, Belgium and Italy. It will take place at the University of Lille, France, at the end of August. The main coordinator of this meeting is Frank Dufour from the French patient organisation: "Vaincre la Mucoviscidose". They have previously organised this much appreciated meeting for French and German young scientists. This year it has been expanded to involve more countries. Meetings like this are needed for young scientists to create their own platform in the CF field and for them to get used to giving oral presentations. The award for the best presentation will be to attend the ECFS conference in Prague 2008 and give an oral presentation in front of a bigger audience.

The most important issue for all of us is the upcoming election. This year we have excellent candidates for the newly constituted election committee and the ECFS board.

Please be active in voting. We need all of you to vote !!

Two years ago when I became president elect for the ECFS I was very happy and had many ideas how to vitalize the society. Thank you to everyone who has made this possible.

I believe personally that the two most important steps are to get a registry and a clinical trial network and we are definitely well on the way to make this happen.

In my mind I had seen myself as your president for either one or two periods, depending on how everything was going.

To be part of ECFS and its energy has meant almost everything for me !!!

However, the working environment in my hospital has become harder and harder for medical doctors. I do not know how it works in other countries in Europe but at least in Sweden we are

having major problems with the administration to make them understand the time and effort we spend on our chronic CF patients. Good CF care costs money and no one wants to pay for that.

We are also having problems with the new working laws from the EU. At my hospital they have solved it so that senior consultants will have to go back into the emergency ward with our young colleagues to work night shift. We will also have to care for pediatric surgery and orthopedics. Personally I am not willing to do this.

In addition, in November 2006 my 20 years old son, Elliot, , became seriously ill. I have had to prioritize Elliot as much as possible, and then I have also come to realize how much time I have spent caring for my patients and not my family.

Ironically in the midst of this negative spiral I was offered a job at the Swedish Medical Product Agency (MPA) as a pediatric specialist involved with the EMEA in London. In this position I have also been given the opportunity to continue as an affiliated professor of pediatrics at Uppsala University which means that I will be able to continue my exciting research on airway epithelium with Professor Godfried Roomans and my PhD students.

Due to the working conditions at my hospital and also, due to my own health and that of my son, I have made up my mind to take on this new challenge.

I do believe it will be a somewhat different tempo and that I hopefully will have more energy left over for myself and my family. I will start my new job as soon as I recover from my illness.

My responsibilities in this new position will preclude any negotiation with the pharmaceutical industry, which conflicts with some of the responsibilities of the ECFS President. The time commitment in this new post will be substantial and involve a lot of travel as I will also have responsibilities in London, at EMEA, as part of their paediatric committee.

Due to all the circumstances mentioned above I have decided to step down as your president of ECFS after our conference in Belek.

I know that many of you will be very disappointed but I hope you understand and respect my decision. I have spent many sleepless nights thinking about this, believe me....

In the interim period 2007-2008 my vice president Stuart Elborn will become your new president. He will do an excellent job with your help and support!! After Belek, the election committee together with the Board will have to work hard to find good candidates for your next president who will then be elected year 2008 during the ECFS conference in Prague.

I realize after this year that it is impossible to be a full time clinician and the president of ECFS (ask my family).

Somehow the society must make it possible for the person who takes on this enormous task to take time off from his/her normal job. Otherwise the president's tasks have to become decentralized and clearly defined between a group of people. The presidency cannot be a one man/woman show

Even if I am no longer your president I will always be there to help you fight CF. I will do whatever I can to facilitate new trials for CF children and drugs in my new role at the EMEA.

I will still be involved in the young scientist meeting in France that is very close to my heart

I am also invited to give a lecture at the EU parliament the 13th of September 2007.

The day is called "Rare Diseases Research: Building on Success". The talk I am supposed to give is "Research on rare diseases in a global context". I am then supposed to cover different fields but I will naturally focus on what ECFS has been able to achieve with the EU project EuroCareCF i.e. our European registry and the Clinical Trial Network.

I told them that I would no longer be your president but they still wanted me to do this.

I promise you that I will make them understand that we are moving forward in a new stronger way through collaboration in the CF field.

Once again be active in your voting. We have five openings for the election committee and four openings for the Board....We need fresh eyes and minds to continue the good energetic spiral....

Hope to see you in Belek

Yours
Marie

Letter from the ECFS Board

Dear Colleagues

You will see from the enclosed letter from Marie Johannesson that she has had a serious illness and is currently unable to work. Since the beginning of March we have taken the decisions relating to the ECFS with help from all members of the board. Subsequently, Marie's appointment to an important post in Medicines Regulation Agency in Sweden, with responsibilities at the EMEA, has been confirmed. This appointment means that Marie has resigned as President for the reasons she has explained in her letter.

We are very sorry to lose Marie from the board as President of the ECFS. We fully respect and understand the decision she has made and wish her every success in her new role.

We assure you that the work of the Society will continue without break. With the help of the ECFS Board we will run the day to day business of the Society. As always, our executive officer Christine Dubois has all the coming meetings well organised and we look forward to the basic science conference in Portugal and the European CF Conference in Belek, Turkey.

There will be a significant number of elections at the AGM this year and the new board and newly elected "Election Committee" will seek nominations for the election of a President at the ECFC in Prague in 2008. In the interim, Stuart Elborn will take on the responsibilities of the President with the support of the board. The wide range of tasks and decisions will be shared by the board to ensure our programme of activities continue without interruption and full participation

in important initiatives such as the EuroCareCF and ECORN-CF is maintained. The new registry is ready to roll out in participating countries and the Clinical Trials network is developing well. These are key projects in the development of our society and we will update you on progress at the European CF Conference in Belek.

Yours faithfully

Stuart Elborn

(Treasurer and Vice President ECFS)

Carlo Castellani

(Secretary ECFS)

The Sixth Ettore Rossi Medal Award

The ECFS is delighted to announce that the sixth Ettore Rossi medal award is to be awarded to :

Dr Edith Puchelle

Reims, France.

Dr Puchelle will receive the medal during the Opening Ceremony of the 30th European CF Conference in Belek, Turkey and will give a short presentation.

Nominations for the ECFS Board

We have received the following nominations for election to the **three** vacant Board member posts.

Dr M Ballman

Head of the paediatric CF- group at Medical School Hannover, Germany

Nominated by Prof M Stern

Dr Harry Cuppens

Associate professor at the Center for Human Genetics, KULeuven, Leuven, Belgium.

Nominated by Prof Margarida Amaral

Dr.Nataliya Kashirskaya

Deputy Chief of CF Department, Russian CF Centre, Moscow, Russia

Nominated by Dr Carlo Castellani

Prof Milan Macek

Chairman of the Institute of Biology and Medical Genetics,

Charles University Prague, CR

Nominated by Dr Hanne Olesen

Dr Anne Munck

CF Paediatric Center Director, Robert Debre Hospital, Paris France

Nominated by Dr Carlo Castellani

Prof. Martin Stern

Universitäts-Kinderklinik, Tübingen, Germany

Nominated by Prof Eitan Kerem

Dr Cornelis Korstiaan van der Ent

Head of department Paed Respiratory Diseases, University Medical Center Utrecht

Nominated by Dr Harry Hjermand

Dr J Walkowiak

Paediatric Gastroenterologist, Karol Marcinkowski

University of Medical Sciences, Poznan, Poland

Nominated by Prof Marie Johannesson

A document containing brief CVs of each candidate together with a ballot sheet, will be sent to members who have paid their current 2007 subscription on April 13th. Mailing will be by email to all members with an active email address. Surface mail will be used where there is no record of an email address or a mailing is returned as undeliverable.

The completed ballot should be returned by surface mail to the ECFS Office. To ensure anonymity and avoid fraud, the ballot sheet should be returned in a sealed envelope with the members name and membership number on the outside. Only three persons should be selected. Ballot papers containing more than three votes will be considered invalid.

Ballot papers must be received by the ECFS Office by the close of business on Friday 29th of May 2007.

Announcement of the results of this election will be made at the AGM

Nominations for the Election Committee

We have received the following nominations for the **five** members of the election committee.

Dr Diana Bilton (UK)

Nominated by Prof S Elborn

Prof. Chris De Boeck (Belgium)

Nominated by Dr Harry Cuppens

Dr. Deniz Dogru (Turkey)

Nominated by Prof A Gocman

Prof Pierre Lehn (France)

Nominated by Prof Claude Ferec

Prof Sanda Nousia-Arvanitakis (Greece)

Nominated by Dr Carlo Castellani

Dr Hanne Olesen (Denmark)

Nominated by Prof Marie Johannesson

Dr Harm Tiddens (The Netherlands)

Nominated by Prof Marie Johannesson

A ballot sheet will be sent to members who have paid their current 2007 subscription on April 13th. Mailing will be by email to all members with an active email address. Surface mail will be used where there is no record of an email address or a mailing is returned as undeliverable.

The completed ballot should be returned by surface mail to the ECFS Office. The ballot sheet should be returned in a sealed envelope with the members name and membership number on the outside. Only five persons should be selected. Ballot papers containing more than five votes will be considered invalid

Ballot papers must be received by the ECFS Office by the close of business on Friday 29th of May 2007.

Announcement of the results of this election will be made at the AGM, and as per the constitution, the committee will serve for the next three years starting with ECFS elections in 2008.

Maurice Super – A Life Dedicated to Cystic Fibrosis



Maurice Super MD FRCP FRCPC. Born Johannesburg 17.10.1936; died 20.09.2006.

It is with much sadness that we report the death of Dr Maurice Super, who lost his battle with leukaemia shortly before his 70th birthday. He will be missed by his many friends, not only in the clinical genetics and paediatric communities, but especially in the cystic fibrosis community, including the many patients he has cared for over the years.

Maurice was born in Johannesburg on 17th October 1936, the son of Eastern European Jewish parents who had first made their home in England before emigrating to South Africa in the 1930s. Maurice attended the King Edward VII School in Johannesburg where he excelled academically and on the sports field, developing his life-long passion for cricket and rugby.

He studied medicine at Witwatersrand University, qualifying in 1959. He trained in Paediatrics in Baragwanath Hospital, Soweto from 1960 to 1966 and became a Consultant Paediatrician with the South West African Health Administration and South African Railways and Harbours in 1967. He was the only paediatrician in South West Africa (now Namibia) for ten years. His interest in cystic fibrosis led to an MD entitled 'Cystic Fibrosis in South West Africa', in which he explored the reasons for the high incidence of CF in the Afrikaans population. Indeed, one of his early papers introduced the hypothesis of population drift and heterozygote advantage as possible explanations.

An example of Maurice's enthusiasm and dedication to the study of CF was the famous 'mosquito tests' in

which he attempted to show that the heterozygote advantage in CF was linked with a reduced incidence of malaria. This involved recruiting CF carriers and 'normal' controls to volunteer to put their bare arms in a box of mosquitoes for several hours and count the bites afterwards: needless to say, Maurice was himself a subject for the experiment! Throughout his career, he remained interested in CF carrier status, with his final research project, continuing throughout his illness, being an investigation of blood pressure in CF carriers and non-carriers.

Maurice's work in Namibia led to a greater understanding of, and an increased interest in, the relatively new field of medical genetics and his next move was to Edinburgh in 1978, where he undertook an MSc in Human Genetics. His MSc dissertation was on the subject of iso-electric focussing of serum proteins in CF patients, the hypothesis being that CF carriers could be detected by their serum protein profiles.

He was subsequently appointed Consultant Clinical Geneticist at the Royal Manchester Children's Hospital where he remained until his retirement in 2001. This appointment, in 1979, was one of the first appointments of a Clinical Geneticist in the NHS. Maurice developed a large paediatric clinical genetic practice and pioneered district clinical genetic clinics through out the North West region. Although busy with clinical commitments, including looking after a large CF clinic with Dr Garry Hambleton, he was able to continue with the iso-electric focussing work, until the arrival in Manchester of Martin Schwarz, a cytogeneticist who was keen to do some DNA work. He persuaded Maurice that DNA (and not IEF) was the way to go with CF, especially as it "wouldn't be too long before the CF gene would be found", and so the DNA lab at RMCH came into being in 1984. As it turned out, the CF gene was mapped the following year, although it was to be a further four years before the gene was finally identified; by then the lab had collected DNA from many CF families and had gained considerable experience in DNA analysis. Maurice's work with families with CF continued in the clinic and in his publication of "Cystic fibrosis; the facts". He established from RMCH a Cascade Carrier Screening Program which continues.

Maurice's keenness to disseminate knowledge about genetics and genetic diseases was demonstrated by the creation of the 'Gene Shop' which was truly ahead of its time. This European funded initiative, developed in association with Ruth Chadwick (then Professor of Bioethics at Lancaster University), was

a public education facility within the shopping precinct of a Manchester Airport terminal. It anticipated the importance of public education about genetics, a function that is now fulfilled by five multi-million pound 'Knowledge Parks', one of which is situated in Manchester.

To work with Maurice for many years and to spend time in his company socially was to know two different men. He was always a supportive colleague and mentor, but at work he was focussed and serious to the point of surliness, whereas outside of work he could be the life and soul of the party, full of amusing anecdotes and with a wonderfully infectious laugh. He and his wife Anne were marvellous hosts, Maurice's bonhomie perfectly complementing Anne's charm and wonderful cooking. His interests were many and varied and could always be relied upon to start the day off on the right foot – just so long as you knew how England were doing in the cricket and precisely why we don't have a bowler like Shane Warne! He loved bridge, and in fact won the Wednesday night tournament at Manchester Bridge Club, home club for many international players, in the week prior to his last hospitalisation. He was a keen bird-watcher, concert goer and tennis player and devoted to a series of dogs.

Maurice's zest for life was reflected in the courage he demonstrated throughout his illness, and his determination to continue to live life to the utmost. He was a man of many passions, but the greatest was always Anne, their children Michael, Beth and Jon, and five granddaughters.

Finally, I would like to place on record my personal debt of gratitude to Maurice, my old boss, mentor and friend, whose influence over my career has been profound – not least in saving me from thousands of hours of microscope analysis! I feel privileged to have worked with him and to consider him and his family as friends.

Martin Schwarz

Training workshop of EuroCareCF (WP7) on: EPITHELIAL CELLS & TISSUES: PRODUCTION CULTIVATION AND CHARACTERIZATION

University of Lisboa (Portugal), 2 - 6 July 2007

This training workshop which will include lecturers, tutorials and hands-on practicals will be open to 20 participants.

Topics:

- Producing and Cultivating Epithelial Cells.
- Characterization of Epithelial Cells and Tissues
- Secretory Trafficking Pathways in Polarized Cells
- Epithelial Tissue Differentiation and Regeneration
- The Early Secretory Pathway and the ER Quality Control
- Regulation Mechanisms of Epithelial Channels
- Physiology of the Epithelial Tissues

Practicals and Tutorials:

- Isolation and Culture of Epithelial Cells
- Transformation
- Immunofluorescence Characterization
- Differentiation and Regeneration
- Functional Assessment of Cultured Epithelial Cells

Lecturers:

- Cristelle Coraux, Reims (France)
- David Sheppard, Bristol (UK)
- Dieter Gruenert, San Francisco (CA, USA)
- Gabriela Rodrigues, Lisboa (Portugal)
- Karl Kunzelmann, Regensburg (Germany)
- Margarida Amaral, Lisboa (Portugal)
- Margarida Barroso, Albany (NY, USA)
- Martin Hug, Freiburg (Germany)

To apply send a CV, letter of motivation and recommendation letter to: Marta Palma (mapalma@fc.ul.pt) until 15 May 2007.

Registration fee: 150 Euro

EuroCareCF web Site

The EuroCareCF web site has recently been extensively revised and update. It can be found at <http://www.eurocarecf.eu/>

We have been asked to particularly draw your attention to the training part of the site found at <http://www.eurocarecf.eu/training.htm>

where there are funding opportunities for training in CF patient care, clinical and basic research. If you know of anybody who may benefit from these training grants, please direct them to contact EuroCare CF via this website.

Workshop on Nasal PD Measurements

To be held in Belek during the 30th ECFC

Title: "Hands on Nasal PD for physicians"

Date: 13th June 2007.

Time: 15.00 – 17.30

By pre registration only with 10 places available

Physicians interested in getting acquainted with nasal PD measurements are invited to attend an afternoon training course. If you are interested to attend send your name and CV to

Christiane.deboeck@uz.kuleuven.ac.be

no later than May 11

Recent Publication on CF

A few of the references have been selected for extra comment due to interesting issues they raise. Initially the reference list has been sent out to a limited number of people but we would like to put together a more comprehensive panel to provide commentaries. If you would like to act as a commentator please contact Dr Ryley (ryleyh@cardiff.ac.uk)

Immunology and Inflammation

Conner GE, Wijkstrom-Frei C, Randell SH, Fernandez VE, Salathe M, AF Conner Gregory E., Wijkstrom-Frei Corinne, Randell Scott H., Fernandez Vania E., Salathe Matthias

The lactoperoxidase system links anion transport to host defense in cystic fibrosis

Febs Letters 2007; 581: 271 - 278

Chronic respiratory infections in cystic fibrosis result from CFTR channel mutations but how these impair antibacterial defense is less clear. Airway host defense depends on lactoperoxidase (LPO) that requires thiocyanate (SCN⁻) to function and epithelia use CFTR to concentrate SCN⁻ at the apical surface. To test whether CFTR mutations result in impaired LPO-mediated host defense, CF epithelial SCN⁻ transport was measured. CF epithelia had significantly lower transport rates and did not accumulate SCN⁻ in the apical compartment. The lower CF [SCN⁻] did not support LPO antibacterial activity. Modeling of airway LPO activity suggested that reduced transport impairs LPO-mediated defense and cannot be compensated by LPO or H₂O₂ upregulation.

Moskwa P, Lorentzen D, Excoffon KJDA, Zabner J, McCray PB, Nauseef WM, Dupuy C, Banfi B, AF Moskwa Patryk, Lorentzen Daniel, Excoffon Katherine. J. D. A., Zabner Joseph, McCray Paul B. Jr., Nauseef William M., Dupuy Corinne, Banfi Bo,

A novel host defense system of airways is defective in cystic fibrosis

American Journal of Respiratory and Critical Care Medicine 2007; 175: 174 - 183

Rationale: The respiratory tract is constantly exposed to airborne microorganisms. Nevertheless, normal airways remain sterile without recruiting phagocytes. This innate immune activity has been attributed to mucociliary clearance and antimicrobial polypeptides of airway surface liquid. Defective airway immunity characterizes cystic fibrosis (CF), a disease caused by mutations in the CF transmembrane conductance regulator, a chloride channel. The pathophysiology of defective immunity in CF remains to be elucidated. Objective: We investigated the ability of non-CF and CF airway epithelia to kill bacteria through the generation of reactive oxygen species (ROS). Methods: ROS production and ROS-mediated bactericidal activity were determined on the apical surfaces of human and rat airway epithelia and on cow tracheal explants. Measurements and Main Results: Dual oxidase enzyme of airway epithelial cells generated sufficient H₂O₂ to support production of bactericidal hypothiocyanite (OSCN⁻) in the presence of airway surface liquid components lactoperoxidase and thiocyanate (SCN⁻). This OSCN⁻ formation eliminated *Staphylococcus aureus* and *Pseudomonas aeruginosa* on airway mucosal surfaces, whereas it was nontoxic to the host. In contrast to normal epithelia, CF epithelia failed to secrete SCN⁻, thereby rendering the oxidative antimicrobial system inactive. Conclusions: These data indicate a novel innate defense mechanism of airways that kills bacteria via ROS and suggest a new cellular and molecular basis for defective airway immunity in CF.

Comment

From the nature of the microbial infection in the CF lung, it has been assumed that there are other deficiencies of the innate immune system and than disruption of the mucociliary escalator probably associated with the CF genetic lesion. A major focus of study has been on possible inactivation of the antimicrobial peptides which are known to be sensitive to elevated salt concentrations. However, there is a growing body of evidence that suggests that the salt level in the CF lung is not elevated over that in the non CF lung. Recently the important role of the lactoperoxidase system in the respiratory tract has begun to be appreciated (Conner et al *Am J Respir Crit Care Med* 2002;166:S57-S61). This is a three component system, lactoperoxidase, exogenous hydrogen peroxide and thiocyanate ions. Lactoperoxidase in the presence of hydrogen peroxide, converts the thiocyanate into hypothiocyanate; an antimicrobial agent that has been shown to be very effective against both *P. aeruginosa* and *S. aureus*. In addition, it appears to have virucidal activity. A similar system exists in phagocytic cells with an analogous enzyme, myeloperoxidase. Recent work indicates that thiocyanate may be the natural substrate for this enzyme as well, although, unlike lactoperoxidase, myeloperoxidase can generate the more tissue-toxic hypochlorous acid from chloride ions.

Two groups have recently independently demonstrated a possible inactivation of the lactoperoxidase system in the CF lung that can be linked to CFTR inactivation. Both have demonstrated using in vitro systems that the CFTR is necessary for the epithelial transport of thiocyanate. By implication there may, therefore, be a deficiency in the CF lung of this ion and the lactoperoxidase arm of the innate immune system rendered inactive.

The implications of these two studies may be widespread providing, as they do, fresh insight into the immune response (or lack of it) in the CF lung. Could some of the experiments previously ascribed to antimicrobial peptide inhibition in fact be due to inactivation of the lactoperoxidase system? Moskwa et al suggest that inhaled thiocyanate might be a useful future therapeutic approach. There are some caveats with regards this. Firstly, sodium thiocyanate is rated as a strong irritant. Secondly, such treatment will probably be less effective in patients with established chronic infections as the superoxide radicals generated will probably be ineffective against colonial biofilms.

Comment by Henry Ryley

CF References

Adults & Adolescents

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Paternity in men with cystic fibrosis: A retrospective survey in France

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