C F Cystic Fibrosis European Network

NEWSLETTER

JULY 2000 – N° 2

NEWSLETTER CONTRIBUTIONS

The closing date for the next issue of the CF Thematic Network newsletter is September 30, 2000.
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EDITORIAL

Dear colleagues and friends,

The CF Thematic Network has started with a lot of enthusiasm and creativity as you will notice from the reports in the present newsletter. It is clear that the scope has changed from a purely diagnostic molecular genetics activity to a more comprehensive approach of Cystic Fibrosis including research, ethical issues and societal issues. We are particularly pleased that the patient organisations and the ECFS are showing a genuine interest in the activities of the network and we hope that this will indeed lead to an improved collaboration between all those involved in the management of CF. While it is clearly not the aim or the purpose of the network to focus on clinical activities, a close collaboration with all those involved in the treatment of CF patients is nevertheless extremely important and valuable for both parties. Indeed only through genuine collaboration will all parties benefit, and the patients in particular, from this unique European expertise brought together in the network. We do hope therefore that we will also get regular contributions from our clinical colleagues for the newsletter.

An aspect of the network that remains to be activated is the industrial partnership. A meeting is scheduled in autumn with a series of company representatives to get this aspect also going. If you are a company representative and would like to participate, let us know.

Finally, some CF research projects that were not selected in the first round will be resubmitted to the EU reviewers in October. We wish them all the best and hope to welcome them early next year in the network.

To all of you, we wish a very pleasant and regenerating vacation.

Jean-Jacques Cassiman
Coordinator of the CF-network
Leuven, July 2000.

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13TH INTERNATIONAL CYSTIC FIBROSIS CONGRESS

The 13th International Cystic Fibrosis Congress was held in Stockholm from 4th to 8th June 2000.

It was preceded by a **Workshop on the taxonomy of Cystic Fibrosis and Related disorders** which was jointly sponsored by WHO, ICF (M) A, the Thematic Network, and the European CF Society, which was convened to make a classification of this group of conditions (largely associated with CFTR mutations) suitable for inclusion in the next edition of the WHO International Classification of Disease (ICD 11) due to be published in 2002. The Workshop did not attempt to correlate genotype and phenotype, and it was emphasised that the diagnosis of CF is still made on clinical grounds, although mutation analysis may help in its confirmation. Other conditions, which may be associated with CFTR mutations, include Congenital Bilateral Absence/Atresia of the Vas Deferens and Recurrent Pancreatitis, but these are not CF and should be separately identified in ICD11. A provisional classification was agreed and a draft document will be sent to the members of the Workshop and some other consultants for approval before submission to WHO later this year.

The **Congress** itself was attended by about 1500 delegates from all parts of the world. Scientific and clinical presentations were of a high quality and reflected the standards of research in progress. A highlight of the meeting was the Joseph Levy Lecture given by Lap-Chee Tsui, who was one of the team who first identified the CFTR gene in 1989.There were no new breakthroughs in science or treatment to be reported, but much steady progress. It was particularly good to see that the prize for the best poster was awarded to a team from Russia, indicating the rapid advances made in recent years within countries of the former Eastern bloc. Elsewhere, among the clinical highlights for this reviewer was the consolidation of experience with inhaled antibiotics, particularly Tobramycin, and the continued interest in fatty acid research. Experience with anti-inflammatory agents such as ibuprofen continues to be promising, but alpha-1-antitrypsin has been disappointing. Treatments aimed at correcting the basic defect, such as gene therapy and focussed pharmacological treatments, are still a long way from clinical use.

John Dodge, Swansea, U.K.

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SATELLITE SYMPOSIUM OF THE EUROPEAN CF THEMATIC NETWORK

One of the planned activities in the project proposal of the European CF Thematic Network was to organise annually a Satellite symposium of the CF Thematic network on the European CF conference. The aim of this symposium was to inform as much as possible participants on the progress of the project, the coming activities, and to bring clinicians, patients and researchers together.
Because the project started last February, the only opportunity to organise a meeting during the International CF conference in Stockholm was an evening session. Nevertheless more than 40 participants were present. The different groups included in the CF network presented their program. The following lectures were held:

Working together in Europe for CF: new perspectives and activities
G. Doering (Tübingen – Germany)

Genetic diagnostic laboratories
E. Dequeker (Leuven – Belgium)

Toward validation of CFTR gene expression and functional assays – A European working group
M. Amaral (Lisboa – Portugal)

CF-related diseases
P.F. Pignatti (Verona – Italy)

Gene therapy approaches for CF
S. Cattani (Munich – Germany)

If it's not CF what do we call it
J. Dodge (Swansea – U.K.)

Informed consent and patent law
P. Saelen (Leuven – Belgium)

The patients and the Thematic Network
K. De Rijcke (CF association – Belgium)

For 2001 we will organise a satellite symposium for the CF Thematic Network during the European CF congress in Vienna (for more information see item meetings). We already have an agreement with the organising committee and they promised a separate session in the afternoon next year. You will hear more in the future.

Els Dequeker, Leuven, Belgium

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ACTIVITY REPORT OF THE WORKING GROUP ON CFTR EXPRESSION

Between April 7th - April 9th 2000 the first Meeting of the Working Group on CFTR Expression took place in Lisboa, Portugal.

One of the aims of the Working Group is the editing of a catalogue of methods and resources in CF research. The catalogue will be publicly available through the section of the Working Group on CFTR Expression on the CF Network web page.

Six subsections were defined:

A - Transcript analysis,
B - Cell biology and histology,
C - Protein biochemistry,
D - Cell physiology,
E - In vivo and ex vivo functional assessment, and
F - Production of models.

A Steering Committee of experts was elected, consisting of: Ann Harris (A), Edith Puchelle (B), Aleksander Edelman (C), David Sheppard (D), Burkard Tümmler (E) and Bob Scholte (F). The task of each member of the Steering Committee will be to review the contributions of the members to the activities of the Working Group within each subsection and in this way to assist as consultants to the editorial work.

June gave birth to the 1st Newsletter for the Working Group on CFTR Expression, in which reports of the meeting are included. In the future the Newsletter will be distributed bimonthly and will also be available through the section of the Working Group on CFTR Expression on the CF Network web page.

The distribution of the newsletter showed a first result: The Working Group grew to the number of 43 members.

Sebastian Beck, Lisboa, Portugal

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THE EUROPEAN CYSTIC FIBROSIS SOCIETY

In 1969, the European Working Group for Cystic Fibrosis (CF) was founded to provide a forum where people from the various disciplines, but with a common interest in CF, could meet, present and discuss their latest findings. Since 1970, there has been an annual meeting (except every four years) in a different European country and organised in conjunction with the local CF association (for past meetings see our web page at http://www.ecfsoc.org). In 1997, the working group was transformed to a Society at the Annual General Meeting held during the 21st European CF conference in Davos. One year later, at the Annual General Meeting held at the 22nd European CF Conference in Berlin, the society was named **European Cystic Fibrosis Society (ECFS).** Due to a conceptional change, the ECFS now organises a major European conference every year.

The ECFS is an independent society, which elects its own officers (for present board members see our web page at http://www.ecfsoc.org). The main objectives of the ECFS are to facilitate the acquisition and distribution of knowledge and to support research into all aspects of CF. This is accomplished by organising annual CF conferences in Europe, by creating committees, working parties or study groups of members under the auspices of ECFS for any purpose related to the objectives of the Society. The integration of the Thematic Network for CF (for details see http://www.med.kuleuven.ac.be/cme/cf/cfnetwork.htm) into ECFS is a good example. The philosophy of the Thematic Network for CF which wants to create a platform for scientists involved in fundamental CF research and other associations harmonises completely with some of the mission statements of the ECFS. ECFS has also established links to the European Respiratory Society.

To ECFS any doctor or scientist engaged in CF research or CF care can apply for active membership of ECFS. The application should be made in writing to the secretary of ECFS. New active members shall be elected at the annual general meeting by the active membership on recommendation of the board of ECFS. Only active members can be elected to the board, the committees, the working parties and the study groups. Any active member has the right to stay in ECFS on retirement as emeritus member. All registered participants in the most recent ECFS congress are corresponding members of ECFS without a vote in the period until the next ECFS congress. National CF associations and commercial companies can become corporate members without a vote (for further details of application see our web page at http://www.ecfsoc.org)

The ECFS will hold its annual conference in Vienna, Austria (5-10 June, 2001); in Genoa, Italy (17-23rd June, 2002) and in Belfast, Northern Ireland (4-7 June, 2003).

G. Döring, President of ECFS, Tübingen, Germany

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EUROPEAN NETWORK FOR CF - PATIENTS POINT OF VIEW

The patient associations certainly welcome any opportunity to communicate and cooperate with groups and individuals that work with the many diverse aspects of cystic fibrosis – such as the Cystic Fibrosis European Thematic Network.

The Network creates a unique forum and opportunity for interaction, exchange and collaboration between CF patients and families and the scientific and medical world and therefore deserves our full co-operation.

One of the major concerns of CF patients and families is proper – *accurate and up-to-date* - information about the disease and the best treatment. With the evolution of internet more and more people have access to all possible sources of information about CF therapy and drugs. There is an urgent need for more and correct information about research, diagnosis and treatment, on what is going on in the different states and research cen-

tres, not only on what will become available on the market, but also on the directions the research is focusing on.

Priorities for the network from a patient's point of view are CF treatment (ongoing research and results on care and treatment, drugs, devices, guidelines for the best possible care and treatment), testing and screening (advantages & disadvantages, ethical and legal aspects, genetic testing and genetic counselling), ethical and legal aspects of gene and biotechnology.

One of the means to establish the communication between the patients and the other parties involved in the network could be an official network website resuming all the above, written by professionals (clinicians and researchers) in collaboration with the patients, presenting their results and methods, addressed to a general public, not only to specialists.

Contact with the patient associations is another means of communication. Right now, several European CF associations are creating a structure to exchange information and experiences about local practices, support offered, etc. As part of this structure we could create a committee responsible for interactions with (in) the network. In our view committees will create a favourable European CF Forum for exchange of information and views between the various groups.

Karleen De Rijcke, Belgian CF Association, Belgium

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REPORT OF THE 1999 EUROPEAN QUALITY ASSESSMENT SCHEMES FOR CF

The 1999 Quality assessment scheme for Cystic Fibrosis was designed to evaluate both the practical analysis (genotype) results as well as the interpretation of the data (the written reports with the test results sent to the physician who asked for the tests).

Six purified DNA samples (harbouring homozygous or heterozygous CFTR mutations) with mock clinical information were sent to 181 registrated laboratories with the request to test them for the presence of *CFTR* mutations using their routine protocols. To ensure anonymity during the whole procedure, an identification number was assigned to each participant by the scheme organiser. The laboratories received 6-8 weeks to analyse the samples and to send the completed results data sheet back to the scheme organiser (genotype results) together with the interpretation of the data. Submission in six languages was allowed (English, French, German, Spanish, Italian and Dutch).

In total 173 laboratories sent the results to the scheme organiser and 86% of these labs sent also the written reports.

A panel of assessors (E. Girodon, M. Schwarz, and M. Stuhrmann) and the scheme organiser (E. Dequeker) evaluated the genotype results together with the raw data and the written reports. The participating laboratories received general and individual comments on their results.

Nine percent of the laboratories incorrectly typed one or more alleles on a total of 12 included in the scheme. As in previous quality assessment schemes (1-2), the genotype errors ranged from administrative errors (35%), technical errors (48%) to misinterpretation of technical correct data (17%). In addition to genotype mistakes, 6% of the laboratories made nomenclature errors. With regard to the interpretation of the data in the written reports, the scheme demonstrated that the way of reporting laboratory results varies considerably between the different laboratories. Unfortunately, 31% of the reports contained errors. 25% of these reports contained administrative errors, like for example typing errors, mostly due to errors against the mutation nomenclature or an incorrect typing of the patient name. Another 25% of the errors were due to mistakes in the risk calculations, which were included. For instance, instead of a risk of 1 in 4 of having a CF child, some reports note 1 in 25 although it might be assumed that the report-writer obviously (and hopefully) meant a chance of 25%. Some laboratories calculated the risk for their particular population, but made mistakes in the calculation. However, in half of these reports, the error was due to a wrong interpretation of the results or the way of reporting. For example, we received reports in which the genotyping results correctly indicated that an individual was a carrier for CF. Nevertheless, a standard report for a diagnosis as CF patient was submitted. Another problem was the lack of the correct reporting of the reason of referral.

In conclusion, the gradual reduction in the error rates of the successive QA scheme for CFTR testing going from 65% of laboratories without mistakes in 1996 to 91% labs in 1999, illustrates the benefit of external QA schemes. However, continued efforts will be needed to further improve the genetic services provided to the community. Therefore we recommend a regular participation of all diagnostic laboratories in external QA schemes, to encourage the personnel involved to participate regularly in specialised training sessions, to introduce consensus strategies for diagnostic testing, to develop a quality system in each molecular genetic diagnostic laboratory leading to accreditation and, in order to centralise mutation analysis for the identification of rare *CFTR* mutations, to set up a network with other CF laboratories in their region.

We advise the laboratories to use the recommendations for quality improvement of genetic testing in cystic fibrosis, which were formulated by the steering committee of the European concerted action of CF and approved by 90 laboratories (3).

E. Dequeker, Leuven, Belgium

(1) Dequeker E, Cassiman J-J
Evaluation of CFTR gene mutation testing methods in 136 diagnostic laboratories: report of a large European external quality assessment
European Journal of Human Genetics, 1998, 6, 165 -175.

(2) Dequeker E, Cassiman J-J
Genetic testing and quality control in diagnostic laboratories
Nature Genetics, 2000, 25, 259 – 260.

(3) Dequeker E, Cuppens H, Dodge J, Estivill X, Goossens M, Pignatti PF, Scheffer H, Schwartz M, Schwarz M, Tuemmler B, Cassiman J-J
Recommendations for the Quality Improvement of genetic testing in cystic fibrosis. European Concerted action for cystic fibrosis
European Journal of Human Genetics, in press.

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THE EUROPEAN CF TWIN AND SIBLING STUDY: CURRENT STATUS

The *European CF Twin and Sibling Study* was initiated in 1995 by the CF research groups from Rotterdam and Hannover with the intention to unravel the cause of CF disease variability and the aim to identify factors that influence CF disease severity. Within the last five years, considerable advances have been made and were reported on in previous ECCACF Newsletters. The objective to identify modulating genetic factors for the so-called monogenic disease CF stems from the well-known observation that (a) while pancreatic sufficiency/insufficiency appears to be determined by the *CFTR* genotype, many other features of the multi-organ disease CF do not show a clear-cut genotype-phenotype correlation that allows to predict a patient's course of disease and (b) when patients with the same *CFTR* genotype are compared, the disease phenotype still shows a broad variation. Apparently, environmental and/or inherited factors besides the *CFTR* genotype determine the outcome of CF disease. Using the clinical data of 86 twin pairs and 454 sibling pairs provided by 223 CF centers from 15 European countries, we could substantiate this hypothesis: The variation in the clinical parameters was comparable for a cohort of patient pairs with the same *CFTR* genotype (i.e.,)F508 homozygotes) and for the cohort of remaining pairs that carry all other *CFTR* genotypes. However, monozygous twin pairs were more concordant than dizygous patient pairs even though these two cohorts were heterogeneous with respect to the pairs' *CFTR* genotypes.

Selection of highly informative patient pairs

The outline of the *European CF Twin and Sibling Study* follows a classical approach to dissect the influence of inherited versus environmental factors on a quantitative trait: by studying CF patient relative pairs, siblings can be compared who share many of their environmental factors, e.g. family environment and their attending physician. Dizygous pairs share on average half of their genes and hence, an intrapair-variation in phenotype might be caused by those loci where the siblings have different genotypes. It is widely accepted that the variability of the phenotype among monozygous twins who are genetically identical is based on environmental factors. Hence, comparing the intrapair variation of dizygous and monozygous patient pairs provides an insight as to whether a trait is determined by environmental or by inherited factors. Taking advantage of the high frequency of the)F508 *CFTR* allele in Mid-European populations, we selected)F508 homozygous patient pairs. Thus, CF disease variability was assessed in a cohort that is homogeneous with respect to the major disease-causing gene. To increase informativeness, we aimed at selecting pairs with extreme phenotypes: from a cohort of more than 300 patient pairs, we identified concordant mildly affected, concordant severely affected and discordant patient pairs. Each of the selected cohorts displayed non-overlapping phenotypes as characterised by two clinical parameters that describe the patients' nutritional and pulmonary status, respectively.

The CF basic defect is variable comparing intestinal tissue from)F508 homozygotes

The basic defect in CF, i.e. defective chloride conductance of CFTR expressing epithelia, was analysed by intestinal current measurement (ICM) of rectal tissue in a micro Ussing chamber (1). The protocol assesses the overall residual chloride secretion and dissects the origin of the chloride secretion by employing DIDS which inhibits non-CFTR chloride channels such as the Ca^{2+} - activated chloride channel but not the CFTR chloride channel itself. We were able to characterise some residual chloride conductance in a third of the investigated)F508 homozygous patients. A DIDS-inhibitable, and hence non-CFTR mediated chloride conductance was observed in 20% and a DIDS-insensitive but cAMP-sensitive chloride conductance was observed in 18% of the)F508 homozygotes. The latter is indicative for functional CFTR in a subgroup of)F508 homozygous CF patients (2). Comparing monozygous twins and dizygous patient pairs, we observed a discordant ICM pattern in a fifth of the dizygous pairs while all but one monozy-

gous twin pair were concordant with respect to the residual chloride secretion. This higher concordance of monozygous twins compared to dizygous pairs points to the role of inherited factors other than *CFTR* in the modulation of the CF basic defect (2).

In summary, even within a cohort that is homogeneous with respect to the *CFTR* genotype, a broad variation of the basic defect is observed. Both, CFTR and non-CFTR chloride channels contribute to residual chloride secretion. Inherited factors other than CFTR appear to determine the eletrophysiological phenotype of)F508 homozygotes.

(1) Veeze HJ, Halley DJ, Bijman J, de Jongste JC, de Jonge HR, Sinaasappel M. Determinants of mild clinical symptoms in cystic fibrosis patients. Residual chloride secretion measured in rectal biopsies in relation to the genotype. J Clin Invest 1994, 93(2):461-466.

(2) Bronsveld I, Mekus F, Bijman J, Ballmann M, Greipel J, Hundrieser J, Halley DJJ, Laabs U, Busche R, De Honge HR, Tümmler B, Veeze HJ and the European CF Twin and Sibling Study Consortium. Residual chloride secretion in intestinal tissue of)F508 homozygous twins and siblings with cystic fibrosis. Gastroenterology 2000, 119(1) (in press).

Candidate gene analysis

The genetic analysis done so far concentrates on a few chromosomal regions which all contain obvious candidate genes for a modulation of the CF phenotype. For instance, ion channels other than CFTR (e.g., the sodium channel ENaC) can be suspected to modulate the CF basic defect and elements of the immune system (e.g. the HLA region) can be suspected to modulate host defence reactions against viral and bacterial pathogens. We have typed polymorph markers near the candidate genes and analysed the allele distribution for an association with the pairs' clinical phenotypes "discordant", "concordant/mild disease" and "concordant/severe disease". So far, within each of the candidate gene region selected, an association of marker genotypes and CF phenotype was detected. Currently, the regions of interest are subjected to high-density marker analysis in order to identify risk haplotypes and/or benign haplotypes and in order to focus the observed effect of allelic association on a specific gene locus. We are looking forward to progress in this approach as the human genome project continues to provide precise information on the localisation of markers and genes on the map of the human genome.

Frauke Mekus, Hannover, Germany

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INFORMED CONSENT AND PATENT LAW (CONTINUED)

Implementation of the EU Biotechnology Directive

(For the relevance of this directive for our research project, see the previous newsletter.) By the end of July all EU member states should have implemented the EU Biotechnology Directive. The next newsletter will contain a survey of which EU member states already have implemented this Directive (…), which member states have implemented it with an informed consent requirement, and which have not. Even when final case applies, the informed consent requirement remains an important issue in patent law. This is because while the national legislator decides what is against Public Order by incorporating an informed consent requirement in patent law or not, it are the national courts who decide on what is against Morality and what is not (for more explanation of Public Order and Morality see the first newsletter). So the debate will continue. One of the questions in this debate is the following:

Is the denial of patent protection an appropriate sanction for inventions based on human body material obtained without informed consent?

One of the preliminary conclusions of our actual research (still in phase 1) is that the discussion of whether or not such an invention should be denied patent protection resembles the dilemma faced by the medical journals for the last couple of years (for example the discussion being held in the BMJ since 1995). For the medical journals it is a question of whether or not to publish the results of medical research studies, which have been conducted without having obtained informed consent.

A denial to publish such studies means denying the authors the scientific appreciation of their peers. A denial to give an invention patent protection has as a result that everybody may exploit the invention, which means denying the inventors the financial rewards of an exclusive exploitation of their invention.

Appeal to send us your informed consent forms

I attended the XIIIth International Cystic Fibrosis Congress and the IACFA Conference Programme in Stockholm. There I have met several patients who were active members either of IACFA (International Association of Cystic Fibrosis Adults) and, or of their various national or regional associations. It was a pleasure for me to meet so many patients who devout so much of their time and energy to their CF-organisations.

During our conversations it became apparent to me that the CF-patients organisations are interested in ethical and legal issues. Patients know that those issues are important for them and want them to be discussed within their own organisations.

For an outsider it could seem strange that the CF-associations have not actually held such discussions (generally speaking). However, one has to consider that CF-patients who are in their twenties, thirties and forties, still constitute a recent phenomenon (the mean age of patients in the European CF Registry is still 14.6 years) and that every association needs time to organise itself.

The CF-Thematic Network and its two ethical-legal research projects offer the patient associations a structured forum where such discussions can be organised. Our research project aims to deal with topics like informed consent, further use of body materials and the legal status of the human body. The research group lead by K. Dierickx and H. Nys will deal with some other ethical and legal topics, like neonatal screening for example (see previous newsletter).

Because this network is on a European scale it would be convenient to have an interlocutor representing the CF-patient-organisations on a European level. This is especially so when our project reaches phase 2, namely the drafting of consensus guidelines on informed consent.

For the moment this is not yet the case, but as a result of different comments done by patients and researchers at the conference, we already appeal towards the patients (organisations), researchers and industry to send or e-mail us copies of the actual informed consent forms you have.

P. Saelen, researcher, Leuven, Belgium

(Promoter: G. Van Overwalle)

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CYSTIC FIBROSIS IN FINLAND - RESOURCE CENTRES, HEALTH CARE AND REHABILITATION

Cystic Fibrosis in Finland

CF is a very rare disease in Finland. With a population of 5.171.300, only 50 Finns, less than 0.001 % have CF diagnosis. Of the 57.600 babies born in one year, one or two are diagnosed with CF.

CF-persons in Finland (31.12.1999)

Age/years	Persons	Female	Male
0 - 5	14	10	4
6 – 11	11	8	3
12 – 17	9	2	7
18 – 23	8	3	5
24 – 34	8	5	3

Resource Centres

Nine separate associations for the disabled have founded Resource Centres for rare and difficult illnesses and disabilities. The Finnish Slot Machine Association provides them with an allowance for their activities.

The Resource Centres work to improve the status of these patient groups by providing services that improve the quality of life and give meaning to life. The Hoikka Centre of the Finnish Association of Pulmonary Disabled (APD) is one of these centres and serves as the National and International Resource and Expert Centre for Rare Pulmonary Diseases. It produces videos and other materials for educational and informative purposes, arranges rehabilitation and adaptation training courses and provides support to those suffering from rare pulmonary diseases, their families and experts.

The most active group by diagnosis is the CF-group. The APD has been arranging activities for CF families since 1983. The CF committee, which was nominated in 1984, has been very active. In 1992, the CF committee was transferred from the head office to Hoikka Centre of the APD.

The Coordinator in Hoikka Resource Centre is a physiotherapist who has been interested in cystic fibrosis for years. She is the Finnish member in the International Physiotherapy Group for Cystic Fibrosis, a group that provides a great deal of important advice about CF physiotherapy from around the world.

CF-persons´ home places in Finland

The coordinator knows almost all the CF-families in Finland personally, and has contacts with experts in hospitals, municipal authorities and the physiotherapists who treat CF-patients. The coordinator hopes that the Hoikka Resource Centre can provide appropriate services to all rare pulmonary disabled individuals and their families. She believes that these activities can help all families to live a normal happy life with their children, even if they have CF or some other serious pulmonary disease.

Health Care in Finland

Finnish health care has always stressed the equal availability of services. The intent has been to provide services to all, regardless of social group, income or place of residence. Municipalities bear the main responsibility for providing health services. Most municipalities provide primary health services through their own health centres, whereas the smallest municipalities form joint municipal authorities for this purpose.

For specialised care, the country is divided into 21 hospital districts (in Turku, Tampere, Kuopio and Oulu there is a University Central Hospital). Helsinki University Central Hospital constitutes a hospital district of its own. The Act on Specialised Medical Care specifies the hospital district to which a municipality must belong.

There are no CF Specialist Clinics in Finland. The University Central Hospitals take care of all patients. For this reason, CF patients use services in their nearest University Central Hospital. The Hospital for Children and Adolescents in Helsinki is the most involved in CF. There are two doctors who have many international CF contacts. They provide information and education to the doctors in other hospitals in Finland.

Rehabilitation

The Social Insurance Institution of Finland oversees the Rehabilitation Programme for Seriously Disabled. Each CF patient receives an individual rehabilitation plan that includes individual physiotherapy, facilities and training equipment needed for self-care, an opportunity to attend rehabilitation or adaptation training annually, as well as facts concerning social security.

Five-day courses for families with CF children take place in the summer with a three-day follow up in winter. The courses for young people last eight days in summer and four days in winter.

The rehabilitation course staff at Hoikka include a doctor (chest physician), trained nurse, physiotherapists, social worker, psychologist, nursemaid as well as other CF experts such as paediatrician, dietician.

Courses for families include discussions of the disease and treatment, nutrition, physiotherapy, as well as about treatment at home, support for families and social security. Additionally, the courses for the young aim to help participants to become independent and to clarify their job possibilities.

Rehabilitation and adaptation courses for families and young people in Hoikka Centre

CF physiotherapy

In Finland, physiotherapists in the hospitals meet CF patients mostly in outpatient departments when the patients have control meetings with the doctor, physiotherapist and dietician. For that reason, the physiotherapists in hospitals have very little experience with CF physiotherapy and treatment. CF patients are very seldom in inpatient departments in hospitals. In addition, intravenous antibiotics can be given daily in the outpatient departments of the hospital, or even in the nearest health centres.

Each CF patient is provided with an individual rehabilitation plan and is treated by a private physiotherapist either at the private institution, or in the CF patient's home. It is beneficial that CF patients are usually treated by the same, their own private, physiotherapist for years.

Leena Jokinen, Coordinator, S.R.PT, Association of Pulmonary Disabled Hoikka Centre, Karkku, Finland.

e-mail: leena.jokinen@hoikkacentre.fi

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ANNOUNCEMENTS

CALL FOR BLOOD SAMPLES OF CF PATIENTS / CARRIERS

In the previous concerted action for cystic fibrosis we started to prepare a library of cell lines harbouring the most frequent mutations of the *CFTR* gene. DNA extracted from these cell lines was used in QA schemes and as appropriate controls in laboratories.

There is a need for more cell lines with different mutations. Therefore I would like to ask to the clinicians who see the CF patients and families to help us to collect samples.

More specifically, we are looking for blood samples of patients / carriers with the following mutations:

Patients and / or carriers with mutation(s) E60X, G85X, 394delTT, Y122X, 711+1G>T, 711+5G>A, 1078delT, R347P, R347H, A455E, Q493X, Q552X, V520F, R560T, 1898+1G>A, 2143delT, 2183AA>G, 2184delA, 2789+5G>A, R1162X, 3659delC, 3849+10kbC>T, 3849+4A>G, S1251N, 3905insT, W1282X, CFTR dele 2,3 (21kb),

Carriers with 621+1 GtoT, W1282X, R117H.

If you can provide a sample, please contact on beforehand the co-ordination centre of CF network, to discuss the practical things.

(Informed consent, environmental conditions of the blood sample, anonymisation of the sample, transport of the sample, reimbursement of the costs). Important to know is that we need fresh blood of the individual (on heparin).

For more information please contact E. Dequeker

International symposium for CF - Budapest December 2 - 3, 2000

In the previous European concerted action for cystic fibrosis we organised annually an international symposium for CF in Eastern or Central Europe (Prague 1997, Warsaw 1998, Ljubljana 1999). Approximately twenty persons were invited to discuss the activities and the needs for genetic diagnostic laboratories in this part of Europe in a separate meeting. In connection with this event, a one-day international symposium was organised for a broader audience.

We will continue this successful activity and the next symposium will be organised in Budapest (December 2 - 3, 2000).

For more information, registration forms, see the web site http://www.med.kuleuven.ac.be/cme/cf/meetings.htm or contact E. Dequeker.

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LEAFLETS

The manual for the CF patients and their families is ready. These leaflets, presently available in English, French, German, Spanish and Italian, were designed to provide cystic fibrosis patients and their families a better understanding of the disease. The manual includes the following topics:

- what is cystic fibrosis
- what happens in the lungs
- what happens in the pancreas
- when to suspect cystic fibrosis
- how is cystic fibrosis inherited from the parents
- to have a child with CF … and to accept a child with CF
- treatment of cystic fibrosis
- hospital
- relatives and friends
- you are not alone

We will send to the CF association in Belgium, Luxembourg, France, Switzerland, Germany, Austria, Spain, Italy, U.K., Ireland and Israel 500 copies. At the end of July, it should also be possible to download the manual from our web page as a pdf file. If you are interested to receive some manuals please contact the coordination center of the CF network or e-mail to CF.network@med.kuleuven.ac.be

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2000 CF QUALITY ASSESSMENT SCHEME

For more information of the QA scheme go to our website http://www.med.kuleuven.ac.be/cme/cf/genetic_diagnostic_labs.htm

The time schedule for the next CF QA scheme is given below.

June - July 2000:
Registration
Laboratories which would like to participate and which are not registered yet, please download the registration form from our website http://www.med.kuleuven.ac.be/cme/cf/genetic_diagnostic_labs.htm
and e-mail or fax it to E. Dequeker
Els.Dequeker@med.kuleuven.ac.be
Fax 32 16 34 59 97

September 2000:
Distribution of the six purified DNA samples which clinical information to the registered participants

December 1, 2000:
Deadline for submission of the genotype results and written reports to the coordinating center

March 2001:
Results and evaluation reports of the CF QA scheme 2000 available

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INGENY

Ingeny International in The Netherlands has been producing equipment for mutation detection for several years. The company is supporting Denaturing Gradient Gel Electrophoresis (DGGE) as a powerful technique for mutation detection. Apart from instruments Ingeny is selling primers for DGGE-experiments for several genes.

For the CFTR-gene primers for DGGE are available for all exons, except exon 9. We supply primers in three different quantities. Quantities are listed according to the number of amplifications they approximately allow. Primers are available in low quantities also, as can be seen below. Dr. Hans Scheffer and Dr. Robert Hofstra, Dept. of Medical Genetics, University of Groningen have designed the primers. The have been well validated by this institute and are in use by several other institutes in Europe.

Through Prof. Dr. Cassiman in Leuven, Belgium we learned that the project in which the institute of Prof. Dr. Goossens in Paris supplied primers to the consortium, has ended. We recognise the importance of primer availability to the consortium, for use in mutation detection using DGGE. Many members of the consortium may have the need to purchase small quantities of primer only. Therefore,

we would like to make a special offer for primers with an emphasis on small quantities. Prices shown are per primer pair. One primer is a short primer of 20 base pairs, the other a long GC-clamped primer with a GC-clamp of between 40 and 60 base pairs, depending on the specific primer design for that fragment.

Number of amplifications	List price in Euro's	Discounted price in Euro's
app. 1000	€ 80	€ 72
app. 400	€ 45	€ 30
app. 100	€ 18	€ 12

Please contact Ingeny for any further information.

For ordering primers the following ordering codes can be used.

IC-CF-1A	IC-CF-1B	IC-CF-13fA	IC-CF-13fB
IC-CF-2A	IC-CF-2B	IC-CF-14aA	IC-CF-14aB
IC-CF-3A	IC-CF-3B	IC-CF-14bA	IC-CF-14bB
IC-CF-4aA	IC-CF-4aB	IC-CF-15aA	IC-CF-15aB
IC-CF-4bA	IC-CF-4bB	IC-CF-15bA	IC-CF-15bB
IC-CF-5A	IC-CF-5B	IC-CF-16A	IC-CF-16B
IC-CF-6aA	IC-CF-6aB	IC-CF-17aA	IC-CF-17aB
IC-CF-6b1A	IC-CF-6b1B	IC-CF-17bA	IC-CF-17bB
IC-CF-6b2A	IC-CF-6b2B	IC-CF-17b2A	IC-CF-17b2B
IC-CF-7aA	IC-CF-7aB	IC-CF-18A	IC-CF-18B
IC-CF-7bA	IC-CF-7bB	IC-CF-19aA	IC-CF-19aB
IC-CF-8A	IC-CF-8B	IC-CF-19bA	IC-CF-19bB
IC-CF-10A	IC-CF-10B	IC-CF-20A	IC-CF-20B
IC-CF-11A	IC-CF-11B	IC-CF-21xA	IC-CF-21xB
IC-CF-12A	IC-CF-12B	IC-CF-21bA	IC-CF-21bB
IC-CF-13xA	IC-CF-13xB	IC-CF-22A	IC-CF-22B
IC-CF-13bA	IC-CF-13bB	IC-CF-23A	IC-CF-23B
IC-CF-13cA	IC-CF-13cB	IC-CF-24aA	IC-CF-24aB
IC-CF-13dA	IC-CF-13dB	IC-CF-24bA	IC-CF-24bB
IC-CF-13eA	IC-CF-13eB		

Orders should be sent to the following address, fax or email:

Ingeny International BV
Amundsenweg 71,4462 GP Goes
The Netherlands

Tel. +31 222 920 - Fax +31 222 923
http://www.ingeny.com - e-mail: info@ingeny.com

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CF NETWORK ON THE WEB

http://www.med.kuleuven.ac.be/cme/cf/cfnetwork.htm

The web site of the CF network has been updated and extended with different pages. For example we added a page with **links to different CF-related web sites**, a page with a summary of the planned **meetings** of the CF network and CF conferences. There is also a new link to the pages prepared for the **genetic diagnostic laboratories**.

We opened also a page for **questions**. If you have a question and you think that someone of the CF network can help you please formulate your question, and send it to CF.network@med.kuleuven.ac.be. The question will be announced on the CF network Question page and the reactions will be published on the site.

Furthermore we created a page where you can search for **the coordinates of European CF network participants.**

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CONGRESSES AND MEETINGS

Under this heading we would like to inform you on congresses and meetings of interest to members of our CF network. If you organise a meeting open for public, please inform us. We will be happy to announce via the CF network newsletter and website. Please inform us also about other interesting meetings not mentioned yet in this list.

ASHG meeting Philadelphia, Pennsylvania, U.S. 3-7 October 2000.
Conference website:
www.faseb.org/genetics/ashg/ann-meet/ashgmeet.htm

North American CF congress Baltimore, Maryland, U.S., 9-12 November 2000.
Conference website: http://nacfc.cjp.com
or e-mail at NACFC@cff.org

ICHG congress
International congress of Human Genetics,
Vienna, Austria, 15-19 May 2001
Conference website: http://www.ichj2001.org
Abstract receipt deadline: December 15, 2000

24th European Cystic Fibrosis Conference
Vienna, Austria, 6-9 June 2001
Conference website: http://ecfsoc.org
or e-mail at congress@mondial.at
Abstract receipt deadline: March 1, 2001

4th Australian Cystic Fibrosis Conference
Brisbane Queensland, Australia, 23-25 August 2001
Conference office: Cystic Fibrosis Australia,
PO Box 254, North Ryde NSW 1670, Australia
or e-mail: general@cysticfibrosisaustralia.org.au

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