ESID Newsletter

Contents

The ESID Newsletter is made for the members of ESID – the European Society for Immuno Deficiencies.

It is published under the responsibility of the ESID Board, and at this moment it is edited by Esther de Vries.

Any ESID member who is interested in publishing his or her views, research, new ideas or other material in the ESID Newsletter is cordially invited to submit copy to the Editor. Suitability for publication is assessed by the Editor in consultation with the other members of the ESID Board.

Editor's address:

Dr. Esther de Vries, pediatric immunologist, Jeroen Bosch Hospital loc GZG, P.O. Box 90153, 5200 ME 's-Hertogen bosch, the Netherlands, tel. +31-73-6992965, fax +31-73-6992948, email esther_de_vries_nl @ yahoo.co.uk .

Dear ESID members,

In this ESID Newsletter, you will find a detailed report on the meeting of the Bone Marrow Transplantation Working Party (Joint ESID/EBMT Inborn Errors Working Party Meeting) containing all the latest news in the field of everyday practice.

Also, you are invited to one (or more if you want!) of the meetings of the J-project, an East-European ESID initiative. You could already find some information about this J-project in the previous issue of the ESID Newsletter.

This time, Switzerland is the subject in the 'Focus on a country' section, and Lithuania in the 'PID-care in development' section. I hope you will enjoy reading these interesting contributions to this issue. **If you have any suggestions for future countries for either of these sections, please let me know!**

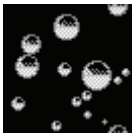
In the President's letter you can read about the efforts of ESID to put PID on the EU agenda.

If you have not yet paid your membership fee, or registered for the ESID meeting in Versailles, please do so as soon as possible! You sure don't want to miss any of the excellent opportunities this offers to you …

Best wishes!

Esther DE VRIES, Editor

P.S. Do contact me at esther_de_vries_nl@yahoo.co.uk about anything you think is of interest for the ESID community that could be published in the ESID Newsletter.



ESID is the European Society for Immunodeficiencies. It was formed in 1994. The forerunner of ESID, the informal European Group for Immunodeficiencies (EGID) was established in 1983. Anyone who is interested in primary immunodeficiency diseases can become a member of ESID. You can find the necessary information to contact the treasurer Esther de Vries at www . esid . org.

Within ESID, six Working Parties are actively engaged in coordinating the member's joined efforts in patient care and research in primary immunodeficiency diseases: Bone marrow transplantation (chair: Andrew Cant), Pathology (chair Fabio Facchetti), Patient registries (chair: Bodo Grimbacher), Clinical (chair: Jean-Laurent Casanova), Genetics (chair: Anna Villa), and Education (chair: Anders Fasth). Anyone who is interested in participating in one or more of these Working Parties is invited to do so. Please contact the chairman of the relevant Working Party (contact information is available at www . esid . org).

In 1994, a main registry of patients with various forms of immunodeficiency in Europe was established. Altogether, data from some 10,000 patients from 26 countries were received until now. In 1995, the first locus-specific immunodeficiency mutation database accessible through the internet was established (BTKbase for X-linked agammaglobulinemia – curators Mauno Vihinen and C.I. Edvard Smith). Since then, several additional locus-specific data bases have been established: ADAbase (adenosine deaminase deficiency – curators Mauno Vihinen and Michael Hershfield), BLMbase (Blooms syndrome – curator Mauno Vihinen), CYBAbase (autosomal recessive p22 phox deficiency – curators Dirk Roos and Mauno Vihinen), CYBBbase (X-linked chronic granulomatous disease (XCGD) – curators Dirk Roos and Mauno Vihinen), CD3Ebase (autosomal recessive CD3 epsilondeficiency – curators Mauno Vihinen and Jose R. Regueiro), CD3Gbase (autosomal recessive CD3 gamma deficiency – curators Mauno Vihinen and Jose R. Regueiro), CD40Lbase (X-linked hyper-IgM syndrome – curators Luigi D. Notarangelo and Mauno Vihinen), JAK3base (autosomal recessive severe combined JAK3 deficiency – curators Luigi D. Notarangelo and Mauno Vihinen), NCF1base (autosomal recessive p47 phox deficiency – curators Dirk Roos and Mauno Vihinen), NCF2base (autosomal recessive p67 phox deficiency – curators Dirk Roos and Mauno Vihinen), RAG1base (autosomal recessive severe combined RAG1 deficiency – curators Mauno Vihinen and Anna Villa), RAG2base (autosomal recessive severe combined RAG2 deficiency – curators Mauno Vihinen and Anna Villa), SH2D1Abase (X-linked lymphoproliferative syndrome (XLP) – curators Luigi D. Notarangelo and Mauno Vihinen), TCIRG1base (autosomal recessive osteopetrosis (arOP) – curators Mauno Vihinen and Anna Villa), ZAP70base (autosomal recessive severe combined ZAP70 deficiency – curator Mauno Vihinen), WASPbase (Wiskott-Aldrich syndrome – curators Mauno Vihinen and Luigi D. Notarangelo) (information is available at www . esid . org).

ESID organizes a biennial congress to facilitate international contact between primary immunodeficiency specialists. The last congress was organised in 2002 in Weimar, Germany; the next congress will be organized in Versailles, France in October 2004, and the one after that will be in Hungary, in 2006.

= ESID Information =

President's letter

European Parliament Hearing on Primary Immune Deficiencies:

On 17th March, a hearing on Primary Immune Deficiencies (PIDs) took place at the European Parliament in Brussels, followed by a reception hosted by IPOPI.

The meeting was organised by the Parliament's Scientific & Technical Options Assessment Unit (STOA), with the support of Baxter.

STOA is an internal committee to advise the EU parliament itself on technical and scientific priorities for the coming year. Prior to the visit, there had been 17 applications for consideration for listing as a priority in the next year (2005). Only 2 were accepted for presentation to the parliament and this was one of those. So, in order to make a report that the Members of the European Parliament (MEPs) could debate, STOA needed to be informed.

This was an open meeting, opened by Professor Antonios Trakatellis, MEP, Chairman of STOA, and chaired by Professor Giuseppe Nistico', MEP.

The European Parliament expert panel at the hearing was composed of: Dr Helen Chapel (UK), Prof Lennart Hammarstrom (Swe), Prof Cees Kallenberg (Net), Dr Janne Bjorkander (Swe), Prof Reinhold Schmidt (Ger), Dr Ann Gardulf (Swe), David Watters (IPOPI), Fred Modell (the Jeffrey Modell Foundation), and myself.

Many members from the European patient organisations, including Teresa Espanol, chairman of the Medical Advisory Panel of IPOPI were also present, as were 28 MEPs and officials, representatives of the Plasma Protein Therapeutics Association, local journalists and members of the general public.

Our common aim was to provide evidence on why primary immune deficiency diseases should be a priority within the EU's Public Health Programme.

Professor Trakatellis welcomed the attendees, underlining the purpose of STOA, which is to serve as a bridge between European society, doctors, scientists, patients and their legislators. The aim of the workshop was to produce a report for consideration by the EU Parliament within a few weeks. It is hoped that this will result in prioritisation of PIDs in the 2005 EU Public Health Programme work plan.

Professor Nistico' has led this proposal himself and we are indebted to him for his interest in our field. His interest stemmed from an admiration of the Network of Excellence on Genetics and, as a Professor of Pharmacology, in orphan drugs. He would like to see a similar network for PIDs which, of course, is ESID. He is keen to build on the previous success of ESID and explained that if PIDs became a priority in the EU's Public Health Programme, this would lead to help for diagnostic methods, data collection and priority in the 7th EU Framework for research, which starts in 2007.

We are hoping that a prioritization at EU level, will support our own case for a greater focus on the needs of patients with primary immune deficiencies within (name of own country). In a world where healthcare budget limitations are forcing governments to prioritize where they spend their budgets, we consider activities such as these as essential if we are to ensure that we have access to resources for research, facilities, education & awareness initiatives and treatment.

As a panel, we presented evidence that PIDs are rare, but life-long diseases, often undiagnosed for many years, with considerable morbidity and mortality. This important workshop was to provide the

detail for the Morbidity & Mortality working party of the Network of Competent Authorities (NCA), which has already expressed an interest in chronic diseases not specifically covered already, in particular immunological diseases. Together, we covered topics including an explanation of PIDs, the estimated prevalence in the EU, how PIDs are treated, the consequences of late or non diagnosis, the benefits of early diagnosis & optimal treatment and lastly, we shared the learnings of the public health approach that has been taken towards PIDs in the US.

An immediate result of the event has been MEPs writing to the European Commission urging them to prioritise primary immune deficiencies, and we will be engaging directly with national health policy makers to ensure they represent our views at EU level to secure this prioritization. A report of the event will be published before the summer, and all information will be posted on the European Parliament website: http://www.europarl.eu.int/workshop/pid/default_en.htm

We are grateful to STOA, and to Prof. Nistico' in particular, for the opportunity we were given to discuss about Primary Immune Deficiencies.

We are indebted to Sophie Ludgate & Karen Wijnant for their help in ensuring that this venture went smoothly and that the issues relating to PIDs were covered comprehensively and comprehendibly by the panel. In the event, it was fun and informative – and the visit to the EU parliament an experience in itself.

Luigi D. NOTARANGELO

Secretary's report

The ESID Board met 27th October, 2003 at Frankfurt Airport. The organisation and scientific program of the Versailles Meeting were discussed in detail. Also, the ongoing efforts for the ESID Registry were illustrated in a presentation by Bodo Grimbacher. The Board will meet again on May 17, in Paris.

Hermann M. WOLF

Treasurer's report

Dear ESID members,

Thanks to all of you who have paid their ESID membership fee 2004/2005. All of you who haven't: please do so as soon as possible, without your contribution to the Society, we will not be able to continue all our projects!

To some of you, I have to explain a bit about how the Treasury works. ESID funds are small, and there is no secretary permanently attached to the Treasury. On an on call basis, I sometimes employ students to do some secretarial bulk work for me, but, small everyday things I have to do myself. This means that it is absolutely *impossible* for me to send you all notices of receival of faxes, emails etc, as you often request me to do. You sometimes simply have to wait a few weeks while membership fee forms accumulate. Once there is a lot of work, I again employ a student, and the work is done!

Of course, we could choose to employ a secretary, but this would mean increasing the membership fee considerably, and I don't think we should do that.

Hoping for your kind understanding!

Esther DE VRIES

News & Views

The J-Project: *TARGU MURES, Romania, Meeting Announcement. Recent progress and future perspectives in PID patient care in Romania.*

Dear colleagues,

We cordially invite you to participate in the Primary Immunodeficiency (PID) Awareness Meeting series starting in Targu Mures, Romania, on March 11-12, 2004. This Meeting entitled „Recent progress and future perspectives in PID patient care in Romania" is part of „THE J-PROJECT" aimed at increasing the level of diagnosis and care for patients with PID in East-Central Europe and to set up a PID Registry in the region (see also ESID Newsletter 2004-1!).

The program was put together as a combined effort of the East-Central European Infectiology and Pediatric Immunology Centre for Training and Research (ECE IPI CTR) and the European Primary Immunodeficiency Program for Newly Associated States (EURO PID NAS).

The meeting in Targu Mures (and elsewhere) will be structured as follows:
- informal discussion in the night before the meeting day,
- introductory lectures mostly by invited speakers,
- case reports mostly by local speakers,
- reports on PID WG and patients group, National Registry Update

The organisers will assure free registration, one night accommodation, and meals for all participants due to generous support by our sponsors: ECE IPI CTR, EURO PID NAS, BIOTEST Pharma GmbH, E S I D , ESPHI.

Organising Committee:

Dr. Maria Cucuruz, Romania Dr. Despina Baghiu, Romania, Dr. Csilla Todea, Romania (csilla_todea@fx.ro), Dr. Zoltan Ellenes,Romania, Prof. Laszlo Marodi, Hungary.

Language: English and Romanian.

The J-Project: *BELGRADE, Serbia and Montenegro, Meeting Announcement. 4th Primary Immunodeficiency Awareness Meeting.*

Dear colleagues and friends,

We invite you to the 4th Primary Immunodeficiency (PID) Awareness Meeting that will take place in Belgrade, Serbia and Montenegro, on June 4-5th, 2004. This meeting is another section of "THE J-PROJECT"

Organising Committee:

Dr. Srdjan Pasic, Serbia and Montenegro (bg.pasic@eunet.yu), Dr. Aleksandra Minic, Serbia and Montenegro, Dr. Jelena Tomic, Serbia and Montenegro, Prof Boris Kamenov, Serbia and Montenegro, Prof. Gordana Bunjevacki, Serbia and Montenegro, Ms Koruga Dragana, YUGOPID chairman (patients organisation), Prof. Laszlo Marodi, Hungary. Language: English and Serbian.

The J-Project: *DEBRECEN, Hungary, Meeting Announcement . Molecular diagnosis of PID in East-Central Europe.*

Dear colleagues and friends,

We invite you to the Primary Immunodeficiency (PID) Awareness Meeting that will take place at Debrecen, Hungary, on August 13-14th, 2004. This meeting is another section of "THE J-PROJECT". The main focus of the meeting in Debrecen will be "Molecular diagnosis of PID in East-Central-Europe".

Organising Committee:

Dr. Melinda Erdős, (meerdos@yahoo.com), Dr. Zoltán Örlős, Rita Ötvös, Judit Szemerédi, Prof. Laszlo Marodi, Hungary. Language: English.

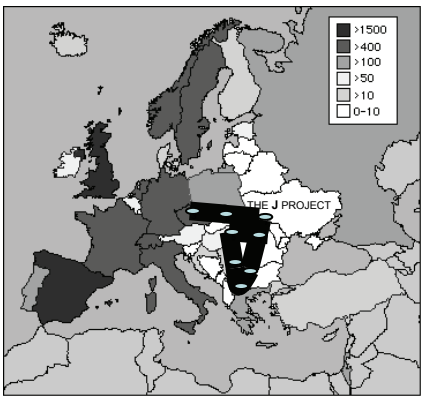
The J-Project: *SKOPJE, Macedonia, Meeting Announcement. Public awareness on PID in East-Central Europe.*

Dear colleagues,

We cordially invite you to participate in the Primary Immunodeficiency (PID) Awareness Meeting series in Skopje, Macedonia, on September 17-18. Our program is part of "THE J-PROJECT". The meeting will take place in Skopje, Macedonia, September 17-18, at the University Children's Hospital, Medical Faculty, Skopje. The major topics will be the current European training programs on Specialisation and subspecialisation in Paediatric Clinical Immunology, the European Network for diagnosis of primary immunodeficiencies, the management of hepatitis C in PID, the improvement of doctor and public awareness and the national registries in the countries of the participants. All these topics, and the possibility of detailed discussion of difficult and unusual cases are of great importance to the improvement of the care for primary immunodeficiencies, particularly in Eastern Europe.

Organising Committee:
Dr. Katarina Stavric, (kstavric@hotmail.com), Dr. Sonja Peova, Dr. Kristina Mironska, Dr. Lidija Kareva, Prof. Laszlo Marodi, Hungary. Language: English.

(For the meetings in Prague, Czech Republic, and Zakopane, Poland, see the ESID Newsletter 2004-1!)



*Proposal for a new Working Party: the ESID**juniors**!*

Dear friends and colleagues,

On September 26th, 2003, during the ESID Summer School 2003 in Portugal we decided to try to form a junior group as a Working Party of ESID.

Arriving a little bit (too) early, sitting around a plate of skate fish and tasting Portuguese beer, the idea to have a better platform for young ESID members rose. We wanted to encourage young people to become ESID members and have an active part in the organisation. We would like to continue the spirit, education and opportunities of the Summer School and take it home to our daily work.

We made a proposal and asked the ESID Board to establish a Working Party called the ESID*juniors,* and to provide the funding to run this new Working Party according to the ESID constitution. The ESID Board members were very enthousiastic about our proposal.

Now, we will ask the approval of the General Assembly of ESID during the ESID Meeting in Versailles, France. Before this meeting we would like to give you an idea about the aims we have.

The main aim is to establish a working group for young colleagues to create a platform for discussions and encourage young colleagues to become actively involved ESID members.

To realize this aim, we formulated the following ideas:

- Establish a chat room on the ESID homepage to exchange experience and to informally pose questions to the ESID*juniors* community on a password protected area. A mailing list should be established.
- Rise problems of junior members that occur in the daily work, i.e. how to deal with patients and problems.
- Address and discuss problems and possibilities of training, exchange

ideas. Point other members to new developments in the field (publications).

- Make an online collection of interesting papers in PID, a collection of links found on the net.
- Share patient histories and results and discuss the next steps, get some ideas by other juniors; collect these cases on a password protected area, for education.
- Get comments from seniors.
- Exchange and offer hosting of other members, organise shared accommodation for conferences.
- Offer other members to arrange meetings or stays in the home labs.
- Establish some kind of funding for colleagues that cannot afford the annual fees.
- Have at least one ESIDjuniors representative in each ESID working party. Everyone can join each working party. One representative of the ESIDjuniors will be elected for two year by the junior members of that working party that is the contact person and will report to the ESIDjuniors community.
- For every ESID meeting local members of the ESIDjuniors will be asked to look after the interests of the ESIDjuniors. One contact person will be elected at the previous conference. Assuming a positive response from the ESID committees, this person should be actively involved in the planning of the meeting.
- Be actively involved in the planning and organisation of the ESID Summer Schools and the educational day at the ESID conferences.
- For the future: create a meeting platform for the ESIDjuniors like local educational weekends.

To become a member of the ESID*juniors* membership of ESID is required. Every ESID member up to the age of 35 years can join the ESID*juniors*. We would also like to have members older than 35 if they are still in medical or scientific training in the field of PID. Members should have a background in PID or immunology and should be in either medical or scientific training. New members are asked to introduce themselves on the website.

The ESID*juniors* will meet biennially at the ESID conferences. The members will elect three members for general organisation, contact and day-to-day work. One of the three will be suggested to the General Assembly to be voted chairperson of the ESID*juniors* Working Party.

On behalf of all the participants of the Summer School 2003, I would like to ask you to take notice of our proposal and to give comments about the proposal if any. The proposal will be presented for vote at the General Assembly of ESID at the ESID Meeting 2004 in Versailles, France. We hope you will all support our proposal for this new Working Party!!

Pim VAN DER VOSSEN

(pwvandervossen@hotmail.com
pvandervossen@alysis.nl)

Working Party reports

Bone Marrow Transplantation Working Party

Joint ESID/EBMT Inborn Errors Working Party Meeting, Paris, 12/13 September 2003:

Over 30 people participated in an excellent meeting superbly organised by Marina Cavazzana-Calvo and held in the Maison de la Chimie. Paul Landais from Paris reported on registry developments and in particular on the useful meetings, seeking to achieve harmonisation of the Working Party's SCETIDE registry forms with EBMT's Med-A forms and hopefully Med-B forms. Paul estimated this would take 12 months. At present however collaboration with the IBMTR did not seem very fruitful as many American centres did not contribute to IBMTR and precise attempts at collaboration have not been successful. The importance of Med-A compliance and accreditation was stressed as was the necessity for ensuring that National and ESID databases were compatible with the SCETIDE database.

The Working Party had 4 sessions:

Session 1 : Long Term Outcome

Wilhelm Friedrich presented data on long term B-cell function in SCID patients transplanted in Ulm. 20/27 patients who received HLA-identical transplants had normal B-cell function as did 32/48 who received non-identical transplants. When those that had received cyto-reductive conditioning were separately analysed, 27/32 given cyto-reductive conditioning had normal B-cell function. There was a suggestion that B-cell function is not so good if an adult donor is used, possibly because there are less B-cell precursors.

Francoise le Deist presented data on cutaneous papilloma virus infections which had been significant in 9 of the 68 survivors of the cohort transplanted between 1971-1992. All 9 patients had had T-B+NK- SCID and the infections had arisen 3-15 years (median 8) after transplantation. These were seen in 3 of the 10 with common γ-chain deficiency and 6 of the 8 with JAK3 deficiency but none of the 2 with IL7 receptor-α deficiency. Bobby Gaspar from Great Ormond Street presented similar data on 7 of their 13 surviving common γ-chain/JAK3 transplant patients; they too had only seen this complication in patients with common γ-chain and JAK3 deficiency. It was thought that the subtle derangement of NK function, or possibly a defect in keratinocytes consequent on lack of common γ-chain and JAK3 signalling accounted for this problem; one case was successfully treated with donor lymphocyte infusions.

Wilhelm Friedrich had analysed the combined data from Paris and Ulm on survival after transplantation for children with SCID due to RAG or Artemis defects. There were 68 patients with 70% long term survival (90% for matched, 60% for mismatched). The survival was 65% for those who had been conditioned and 45% for those who hadn't. Looking more closely at the mismatch transplants, all 6 of the RAG patients who received no conditioning died whereas 85% of those receiving conditioning survived. For Artemis, 45% of those who received no conditioning survived compared to 65% who received conditioning. These data highlight the necessity for conditioning in these patients. Interestingly, one Artemis defect patient presented with Omenn's syndrome.

Despina Moshous then presented the 10 year experience of MUD transplantation for primary immune deficiency from Brescia. 39 patients have been transplanted since 1992. 32% for SCID, 24% for Wiskott-Aldrich, 18% for CID. 66 searches lead to 39 BMTs (59%). The median time for waiting was 74 days for SCID and 156 days for others. 27 searches were aborted, 2 because of parental refusal, 17 on clinical grounds (15 of these patients received

haplo-identical transplants), 2 because the patients were given PEG-ADA, 5 because the patients died and 1 because there was no donor. 8 of the transplants were 5/6 matches and 31 were 6/6. Conditioning was mainly with Busulfan and Cyclophosphamide. 8 patients developed grade 3 GvHD or greater. 30/39 survived. Deaths were mainly due to infection. This compared to 90% survival with HLA-identical transplants and 60% for Haplo-identical BMTs. There was a discussion about using MUD in SCID transplants, and how long it was reasonable to wait before embarking on a SCID transplant. Overall, the results from haplo-identical and MUD transplants seemed similar although without doing a controlled randomised trial it was not possible to definitively answer this question.

Bobby Gaspar briefly mentioned the long term ADA-SCID outcome study and will be asking centres for more details on metabolic outcome.

Session 2 : New Techniques

Paolo de Coppi gave a presentation on fetal membranes as a new source of totipotent stem cells. These cells could be isolated from amniotic fluid or placenta, and differentiated into osteoblasts, adipocytes, myocytes, endothelial cells, hepatocytes, and neuronal cells.

Annet Van Royen then reviewed the American data on mesenchymal stem cells for the treatment of osteogenesis imperfecta and Hurler syndrome (with regards to neurological and skeletal defects). There was discussion as to whether low intensity conditioning would work, as full intensity was necessary for other metabolic conditions. It was questioned as to whether the 1% donor chimerism achieved was enough to correct mesenchymal cell defects and how much benefit had been seen in the American patients treated so far.

Sophie Caillat-Zucman presented data on NK alloreactivity, firstly succinctly reviewing the work on KIR epitopes and NK alloreactivity, and then a study of 46 BMTs in 41 patients with primary immune deficiency. 27 were KIR mismatched and 17 matched. Somewhat surprisingly, there was no difference in engraftment, GvHD, secondary rejection, or full donor chimerism. It was concluded that it had not been possible to reproduce the results seen in Perugia's leukaemic BMT patients, possibly because the patient group was difficult or because the Perugia data came from adults. Further work is needed.

Isabelle Andre-Schmutz presented very elegant studies on depletion of alloreactive T-cells by activating alloreactive T-cells in an MLC and then binding anti-CD25 monoclonal antibody to the activated cells and so removing them. In a trial involving 25 patients undergoing haplo-identical bone marrow transplantation who were given between 6x10^5 and 1x10^7 T cells/kg and ATG between day -14 to day -10. A significant survival advantage has not yet been shown, but further work looking at the level of residual reactive cells and the size of the T-cell add back is being pursued. Other groups reported collaborative work looking at different methods of allodepletion and in particular whether 2 allodepletion steps were needed.

Session 3 : Guidelines / Outcome

Reinhard Seger led a discussion on BMT for Chronic Granulomatous Disease. He first described some animal experiments showing that the neutrophil oxidative burst is needed to clear inflammatory cytokines and that failure to clear these cytokines increased pneumonitis after bone marrow transplantation. There were other experimental data which suggested that anti-CD52 could block an allo-mixed lymphocyte reaction by destroying monocyte derived dendritic cells which could phagocytose antigen. For these reasons, he proposed that anti-CD52 monoclonal antibody would be better than ATG in the BMT conditioning protocol. There was then a discussion about the best form of conditioning for patients with inflammatory disease at the time of bone marrow transplantation. There was a

proposal to use Busulfan 8mg/kg and Fludarabine 180mg/m2, but it was concluded that it would be better to keep using the current agreed protocol with Fludarabine and Melphalan until sufficient patients had been recruited. The use of MMF for 28 days post transplant as rejection prophylaxis for high risk patients was discussed. Campath 0.3mg/kg day -4 to day –2 will also be used for high risk patients with an HLA-identical donor.

Nathalie Gartier and Colin Steward reported on indications for BMT in X-linked adrenoleukodystrophy. Their most important conclusion was that there must be no neurological impairment before bone marrow transplantation.

Nico Wullfraat reported on the European study of BMT for autoimmune disease. In the new Windsor protocol either peripheral blood stem cells or bone marrow can be used, with CD34 positive selection and between 0.5 and 1.10^3 CD3 positive cells and > 1x10^6 CD34 positive cells would be given. Conditioning would be with ATG, Cyclophosphamide and Fludarabine and no patients would receive radiotherapy as analysis of the previous study showed that this brought no benefit. Supportive care would include IVIG until the CD4 count was > 500 cells/µl and there would be PCP and anti-viral prophylaxis for 6 months.

Hülya Özsahin reported on the long-term follow-up of BMT for Wiskott-Aldrich syndrome. Twelve centres reported data on 110 patients transplanted between 1972-2001. Overall 74 (67%) of patients survived, (73 cured), with survival being 88% for HLA-identical transplants, 71% for MUD transplants and 44% for haplo-identical transplants. Both HLA-identical and MUD transplant patients had a high instance of full donor chimerism although this was slightly less for haplo transplants. Of 73 patients 8 had on-going autoimmunity and 19 various clinical complications though none needed platelet transfusions.

Paul Veys reported on low intensity transplants for primary immune deficiencies comparing 33 patients who received such transplants through October 1998-January 2002 with 19 patients who received transplants after conventional myelo-ablative conditioning between 1994-1998. Overall, 31/33 patients with low intensity conditioning (93%) survived compared to 12/20 (60%) with myelo-ablative conditioning. Survival after low intensity conditioning was increased in non-SCID patients but not in SCID patients. Low intensity conditioning was associated with less good chimerism especially after mis-matched unrelated donor transplants but the incidence of GvHD was very low. There were more viral infections in the lower intensity conditioning group. There was then an extensive discussion about the results. Overall, the results looked very encouraging but it was important to note that the myelo-ablated group was a historical control group. During the last 10 years, results for transplantation for primary immune deficiencies all improved. It was therefore a moot point as to whether the improved survival was purely due to the use of low intensity conditioning or to better supportive care in general. There was discussion about whether MMF post-transplant would decrease rejection following low intensity transplantation, and when to use Rituximab during EBV-reactivation following low intensity conditioning; it was suggested that Rituximab could be used if there was an EBV viral load of > 10^5µ/l by PCR. It was also suggested that fever was an important clinical sign of significant EBV disease.

Colin Steward led a discussion about the treatment of pulmonary hypertension after bone marrow transplantation for osteopetrosis and presented data that demonstrated the efficacy of Prostacyclin using doses up to 35 µg/kg/min, tapering off over several weeks as the symptoms resolved.

Anders Fasth then reviewed Di George syndrome pointing out that severe T-cell immune deficiency was extremely rare, occurring in probably 1/100 Di George

patients. There was an overlap between patients with 22q11 deletions, 10p deletions and CHARGE association co-existing with SCID.

A proposal to carry out a study of prophylactic defibrotide in the prevention of VOD was discussed but it was concluded that probably this would be better done in treating children with conditions such as neuroblastoma where the incidence of VOD was much higher.

Andy Gennery and Graham Davies then reviewed the European data on BMT for CD40 ligand deficiency in 38 patients. 34 patients engrafted and 26 (68%) survived. Of these 22 were cured of their disease, and none of these were on IVIG replacement. The 12 deaths all related to infection. Draft guidelines on which patients with CD40 ligand deficiency should receive a BMT included patients with an HLA-identical sibling donor, possibly all patients with a matched unrelated donor and certainly those who had signs of early complications. Mis-matched unrelated donor BMT should probably only be used when there were definite early complications and haplo-identical BMT reserved for cases with progressive organ damage. Complications were defined as liver or lung damage, enteropathy, neutropenia not responsive to IVIG or cryptosporidial infection. If there was no organ damage, then it was proposed to use conditioning with Busulfan, Cyclophosphamide or Fludarabine and Melphalan. If there was organ damage, it might be wiser to use Fludarabine and Melphalan although the study to-date has not shown an absolute benefit for this. Haplo-identical transplants should be planned on an individual patient basis. The importance of prophylaxis and treatment of cryptosporidium using Azithromycin, Nitazoxanide and Paromomycin was highlighted, using Azithromycin alone if the stool cryptosporidial PCR was negative, or Azithromycin and one other agent (probably Nitazoxanide) if the PCR was positive, and Paromomycin should then be added when cryptosporidiosis was clinically apparent. The potential ototoxicity of Paromomycin was noted.

Paul Veys led a brief discussion on JACIE accreditation. In Europe, certain countries were very keen that there should be extra paediatric standards whilst others were not. It looks as if this is proceeding on a country by country basis.

As is usual at Working Party's an hour and a half was spent discussing interesting cases which was helpful.

Session 4 : Gene Therapy

Alain Fisher detailed the French experience of 10 cases of γ-chain deficiency in SCID treated between the ages of 1-10 months with between 1 and 22x10^6 transduced cells/kg. 1 patient did not engraft and needed a rescue BMT. 2 patients developed lymphoproliferative disease, 1 of whom is in complete remission after 1 round of chemotherapy, the other is well but with some abnormal cells after 2 rounds of chemotherapy and an unrelated bone marrow transplant. The remaining patients have developed very good immune reconstitution and with on-going production of transduced cells as evident by TRECS studies. B cell function was present in all patients but incomplete in 3; 1 patient was on IVIG. In 1 teenager the process did not work (? Absence of thymic function). In 1 patient it probably didn't work because all of the engrafted cells settled in the spleen. The lymphoproliferation was associated with activation of the oncogene LMO2 because of integration at that site. Marina Cavazzana-Calva and Alain Fisher are carrying out very detailed animal studies to look into this further and have suspended their clinical programme until these are complete.

Adrian Thrasher described their experience of gene therapy for X-SCID in 5 patients, in one 20 year-old patient there was no effect at all. In the other 4 patients there was good reconstitution. There was then a discussion as to which patients should be considered for gene therapy, especially in the light of the very

good results from haplo-identical BMTs. Generally it was agreed that young patients probably should have haplo-identical bone marrow transplantation but perhaps there was a case for older and more poorly patients receiving gene therapy.

Alexandro Aiuti described the Milan experience in 4 patients given gene therapy for ADA-deficient SCID. In each case, Busulfan at 2mg/kg/day for 2 days was given on day - 3 and day - 2, marrow having been harvested on day - 4. No patients had received PEG-ADA prior to transplant. Patients were given between 0.9-8.6x10^6 CD34+ cells/kg. Post-therapy, the patient with the lowest dose of CD34+ cells had the lowest B cells. Spectrotyping and proliferations were normal in all patients. 2 patients were off IVIG. Transduced cells were found in myeloid and progenitor cells at between 5-10% of 2 patients, at 1% in 1 patient and at a trace in another. No integration sites were close to LMO2.

Naomi Taylor then described animal work in the ZAP70-kinase knockout mouse to look at the possibility of gene therapy in this condition. She pointed out that when gene therapy studies were carried out in mice it was mainly in adult mice who had been irradiated and the CD34 cells were selected by killing the others with the 5FU. Furthermore, the genetic strains of mice used (C57/B16) had a TH1 skew with a high risk of malignancy, and were kept in a germ free environment. She was now carrying cells in young mice with a lentivirus vector.

Further Action

Different members of the Working Party agreed to review protocols and circulate to members of the group before returning to Marina and Andrew by 30th November 2003, so that they could be promulgated by the end of December 2003:

SCID and CID - Wilhelm Friedrich and Suzanna Müller,
CGD - Reinhard Seger and Terry Flood,
CD40 Ligand - Graham Davies and Andy Gennery,
Osteopetrosis - Colin Steward,
HLH - Alain Fisher.

Ongoing Studies / Recent Publications

The Working Party engaged in 10 ongoing studies, including:

BMT protocols for high risk CGD,
Peripheral stem cell transplants in SCID,
Comparison of SCT in RAG and Artemis deficient SCID,
BMT in Omenn's syndrome,
Comparison of myeloablative and non-myeloablative conditioning in URD SCT.

Recently published or accepted papers include:

Seger RA, Gungor T, Belohradsky BH, Blanche S, Bordigoni P, Di Bartolomeo P, Flood T, Landais P, Muller S, Ozsahin H, Passwell JH, Porta F, Slavin S, Wulffraat N, Zintl F, Nagler A, Cant AJ, Fischer A. Treatment of chronic granulomatous disease with myeloablative conditioning and an unmodified haemopoietic allograft: a survey of the European experience (1985-2000). Blood 2002;100:4344-50.

Antoine C, Müller S, Cant AJ, et al. Long-term survival and transplantation of haemopoietic stem cells for immunodeficiencies: report of the European experience (1968-1999) The Lancet 2003;361:553-60.

Gennery AR, Khawaja K, Veys P, Bredius RGM, Notarangelo LD, Mazzolari E, Fischer A, Landais P, Cavazzana-Calvo M, Friedrich W, Fasth A, Wulffraat NM, Matthes-Martin S, Bensoussan D, Bordigoni P, Lange A, Pagliuca A, Andolina M, Cant AJ, Davies EG. Treatment of CD40 Ligand deficiency by haemopoietic stem cell transplantation: a survey of the European experience (1993-2002) Blood October 2003 (online publication).

Andrew CANT

Genetics Working Party

In the previous ESID Newsletter, I asked if anybody was interested in the analysis of a possible correlation between genotype and phenotype of some PIDs. Unfortunately, I did not receive any suggestions from you, the clinicians. Laboratories as ours, which are involved in the study of basic mechanisms of diseases sometimes are not able to deeply understand the clinical differences due to different mutations in proteins. For this reason, the dialogue between clinicians and researchers is crucial to reveal some unexpected characters of the studied molecules. As I did not receive any comments, I would start from a disease studied by our group, Infantile Malignant Osteopetrosis.

I would like to see if there is any correlation between the gene involved in the disease and the follow-up of OP patients after bone marrow transplantation. I invite all clinicians interested in the analysis to contact our group! (Anna.villa@itb.cnr.it)

Anna VILLA

I also would like to focus your attention on an interesting workshop on ATM defects: International AT Symposium, 8-11 June 2005, Hotel Villa Carlotta, Belgirate, Lago Maggiore.
Chairmen: Luciana Chessa, Domenico Delia.
Scientific Committee: Jiri Bartek, Pat Concannon, Jean Gautier, Dick Gatti, Janet Hall, Martin Lavin, Peter McKinnon, Malcom Taylor, and Yossi Shiloh.

If you are interested, you can contact Dr Domenico Delia, Dpt. of Experimental Oncology, Istituto Nazionale Tumori, email: domenico.delia@istitutotumori.mi.it

Clinical Working Party

Please remember the ADA-survey in the ESID Newsletter 2004-1! If you have not yet completed it and returned it to Bobby Gaspar at fax 44 207 831 4366 or email h.gaspar@ich.ucl.ac.uk, please do so as soon as possible. The more people react, the more useful the results will be.

Jean-Laurent CASANOVA
Bobby GASPAR

Also, the effort of establishing an ESID protocol for the diagnosis of suspected PID is nearing completion. So far, the following people have sent their comments to Esther de Vries at email esther_de_vries_nl@yahoo.co.uk: Andrew Cant, Jean-Laurent Casanova, Domenico de Mattia, Brian Eley, Alina Ferster, Anete Grumach, Marja Helminen, dr. Kumararatne, Taco Kuijpers, Baldassarre Martire, Françoise Mascart, Asbjorg Stray-Pedersen, Sirje Velbri, and Krzysztof Zeman.

If your name is not on the list, and you did send a reaction, please let me know at once!

If you want to participate in this effort after all, please send me an email, and I can send you the latest version of the protocol for comment.

Esther DE VRIES

Focus on a country:

Established member Q&A
Reinhard Seger
Dept Paediatrics
University Children's Hospital
Zurich, Switzerland

Can you give me some information about your background and can you tell me something about your career history?

I was born and grew-up in Berlin and went to high-school in Addis Abeba, Ethiopia, where my father worked in a German development project. After my medical education, again in Berlin and in Lausanne, Switzerland (where I learned to ski and speak French!), I went to London to obtain a diploma in tropical medicine with the intention to return to Africa. However, things turned out differently. In London, I discovered that infections have two sides like coins, invading microbes and - most fascinating - host defence mechanisms. So, I changed my plans and was very lucky to gain a place in the only British MSsc course in Immunology at that time, in Birmingham. My research project was allogeneic neonatal thymus transplants into nude (athymic) mice. I had to test whether the nude bone marrow stem cells would differentiate into new T-cells tolerant of the foreign thymus. After these decisive two years in experimental immunology, and after meeting Prof. Hitzig my new goal became clear: to become a paediatric infectiologist/ immunologist.

I obtained my paediatric training at the University Children's Hospital in Zurich, where I then worked as paediatric infectiologist. This was followed by another decisive 1,5 years of further training in clinical immunology with Claude Griscelli in Paris and Rebecca Buckley in Durham. Very fortunately, Alain Fischer was chef-de-clinique in Paris at that time and taught me the art of bone marrow transplantation, an exiting and promising tool to treat congenital blood disorders and immune deficiencies not yet routinely performed in Switzerland. Back in Zurich, with all this experience, I succeeded Prof. Hitzig in 1989 as head of the Division of paediatric immunology/haematology in 1989 and became a Swiss citizen and professor in our faculty.

How did you become interested in immunodeficiencies?

During my medical studies in Berlin in the late sixties, the field of immunology did not exist. I had no lectures in immunology, except for antimicrobial antibodies and the tuberculin skin test. It was only during my MSc course in Birmingham that I learned about the existence of B- and T-lymphocytes and various other components of the immune system. Nude (athymic) mice were the first immunodeficient 'patients' I encountered! Although the ultimate cause of their immunodeficiency was completely unknown, they could be saved from a dismal fate by simple thymic transplants, once and forever!

Later, in Walter Hitzig's division I cared for real patients with PID. Although the basis of their genetic defects was again unknown, it was fascinating for an infectiologist to observe that similar related defects in cell function resulted in similar patterns of opportunistic infections. Therapeutically, the severe and often lethal clinical courses of T-cell and phagocyte deficiencies were most challenging! How could one circumvent the cellular defects or replace the defective cells? I found the prospects of cellular engineering most exiting and that's why I entered the field.

What have been your achievements in research and patient care in the field of immunodeficiencies?

In a small country like Switzerland (with only 7 million inhabitants) primary genetic diseases like immunodeficiencies are rare, even with national referral. The key "survival" factors of our small centre turned out to be:
1. Association of paediatric immunology with a more important clinical activity: BMT.
2. Focused active research using a defective immune defence mechanism as model for more frequent diseases: Innate Immunity
3. Persistence of the 'umbilical cord' linking us with a bigger European centre for immunodeficiencies: Paris.

My group (Françoise Berthet, Peter Tuchschmid, Hülya Özsahin, Tayfun Güngör) has established paediatric BMT for the whole range of indications in Switzerland, which keeps us busy and results in national referral of all serious immunodeficiency diseases. We were among the first to perform successful stem cell transplants for the immunodeficencies of cartilage-hair hypoplasia and dyskeratosis congenita (using non-myeloablative conditioning). After describing the improved yield and function of G-CSF stimulated donor granulocytes for transfusion (Blood 1993) we could publish the first report of successful BMT for a CGD-patient with therapy-refractory multifocal aspergillosis (Blood 1998) using this support.

After expanding the immunology laboratory of Walter Hitzig with a granulocyte research lab, chronic granulomatous disease became the most common PID in Zurich. We could show that two successful antibiotics in CGD owe their success to lipophilic uptake (co-trimoxazole) (Ped. Res. 1981) or active transport mechanisms (fosfomycin) (Ped. Res. 1985) into the killing-deficient phagocytes. Later, a number of new mutations in the gp91phox, p22phox and p67phox genes were functionally characterised (in close collaboration with the group of Dirk Roos in Amsterdam).

In the last 10 years, our research (Johann-Peter Hossle, Sandra Saulnier) has focused on the development of a clinical protocol for gene therapy for CGD (in close collaboration with the group of Manuel Grez in Frankfurt). After establishing a vector active in human myeloid stem cells (Human Gene Therapy 1998) and promising reconstitution experiments in X-CGD mice (Human Gene Therapy 2003) a clinical trial is starting in Frankfurt, London (Adrian Thrasher) and Zurich with the first results hopefully available by the end of the year.

Since my specialist training, there has always been a close and most enjoyable cooperation with the immunodeficiency/ BMT centre in Paris resulting in a unique exchange of research ideas and clinical experience. Those who profit most from this vital 'umbilical card' are the Swiss patients, since rare diseases are seen once a year in our country and 10-20 times a year in Paris.

What kind of developments in immunodeficency do you expect in the near future?

Without being a prophet, at the moment I can see three promising directions.

First, the identification of new "disease-causing" genes, especially in the field of innate immunity and autoinflammatory syndromes, long neglected by classical immunologists. The work of Jean-Laurent Casanova and Daniel Kastner points the way.

Second, the understanding of the molecular roles of newly identified gene products in signal pathways, btk and WASP just being the top of the iceberg. A comprehensive view could result in true pharmacological interventions.

Third, the development of effective and safe strategies of gene therapy. How can one ensure enable engraftment of transduced cells which lack selective growth advantage (such as in CGD)? And how can one promote directed integration of retroviral or non-viral-vectors in "harmless" chromosomal locations?

With all these developments, todays'

PID services will evolve into highly specialised treatment centres for molecular defects in immune defence and immunoregulation.

What is your advice for young people who want to launch their career in immunodeficiency?

A career in immunodeficiency remains an individual journey full of adventures. Members of our generation prepared themselves with an education in immunobiology which is no longer sufficient, since the era of molecular medicine has begun. Today, a thorough MDPhD study in the field of molecular genetics and molecular cell biology would be the best investment. I would then obtain further subspecialty training in one of the few centres of combined excellence in research and patient care. As in the past curiosity - both at the bedside and at the bench - careful observations with a prepared eye as well as disbelief in dogmas and authorities (!) are the road to new discoveries.

And – last but not least – what does ESID mean to you?

ESID has become the most important forum (or better home) for clinicians and scientists involved in PID, from Europe, and increasingly also from America. When you attend the 2-year-meetings, you will be updated on all major developments from molecular to therapeutic immunology. Fortunately, ESID is not elite, but wide open to anybody interested. For me, ESID is a model of how European countries should collaborate in medicine, with active Working Parties, ongoing multicentre studies and functioning clinical and mutation registries as well as long-lasting friendships resulting from these collaborations. In addition, the Summer Schools – Helen Chapel's initiative – provide excellent and pleasant education to young investigators, and will hopefully recruit as many as possible into our exciting field.

Young Investigator Q&A
Sonja Junge
Dept Paediatrics
University Children's Hospital
Zurich, Switzerland

Can you give me some information about yourself and your background?

I am 29 years old and was born in the small town of Tübingen located in Southern Germany, close to the black forest and the lake of Constance.

Can you tell me something about your career history?

I studied Medicine at the Eberhard-Karls-University of Tübingen, and spent one year of my studies at Aberdeen University in Scotland. Being interested in the field of immunology I committed myself to my thesis at the University of Tübingen, at the Institute of Physiology of Prof. Lang, in the laboratory of Prof. Gulbins. This was the time when I first got involved in experimental medicine. After my graduation, I did an internship with the World Health Organization in Geneva focusing on children's health problems. Since July 2002, I have been following my clinical pediatric training at the University Children's Hospital of Zurich, while being engaged in a scientific project of the department of immunology under the

guidance of Prof. Seger and Dr. Güngör, aiming at the investigation of immune reconstitution after bone marrow transplantation in children.

How did you become interested in immunodeficiencies?

In the final year of my medical studies, I had the opportunity to work on the bone marrow transplantation unit of the University Children's Hospital of Zurich where I was fascinated by the integrated approach clinicians were taking in order to treat severely ill children. Basic research and its clinical application seemed to be interdependent. This was a very enriching experience to me.

What have been your achievements in patient care and/or immunodeficiency research up to now?

In my thesis, we could elucidate critical steps in the signaling cascade of the adhesion molecule L-selectin and shed some light on its role in inflammatory processes. A case of a patient being transplanted for leukocyte adhesion deficiency illustrated the relevance of a better understanding of leukocyte adhesion mechanisms and defects. In the last year, we were looking in detail into the immunological reconstitution of bone marrow transplanted children. We established tools to measure thymic function and learned more about the characteristics of recent thymic emigrants and the reconstitution of T cell immunity.

What do you hope to achieve in the future?

We would like to test our hypotheses about the reconstitution of the innate and adaptive immune system in clinical settings in order to better understand the complex pathways our immune system is taking in health and disease. Further experimental and clinical research needs to be done to provide us with the necessary knowledge to improve patient care.

How are you planning to reach this goal?

Only collaboration of all knowledgable parties - clinicians, basic researchers and policy makers - may put together the strength to tackle crucial immunological problems. The key condition for a fruitful collaboration is an effective communication between those involved. By gaining experience in the field of clinical medicine as well as in basic research I would like to contribute to bridge the gap between these complementary disciplines.

And - last but not least - what does ESID mean to you?

ESID is a very important platform to get in contact with leading physicians and biologists interested in the field of immunodeficiencies. I hope to be able to take part in one of the ESID Summer Schools for my further immunological education!

What would you want to change if you were president of ESID?

I would like to intensify collaboration between hospitals and laboratories associated to ESID in order to create vivid interaction between young scientists.

PID-care in development:

Can you give me some information about your background and can you tell me something about your career history?

My name is Rasa Duobiene. I was born in January 1964, in Vilnius (the capital of Lithuania). From my early childhood, I have been close to a medical world since my mother worked as a paediatrician. Still, as a schoolgirl I began my medical career at the Vilnius University Children's Hospital, where I had an auxiliary's duties and later, during my studies at the University, I worked as a nurse at the same hospital. In 1998, I graduated from the Faculty of Medicine at the University of Vilnius and was qualified as paediatrician. After the internship, I had a few years' maternity leave. My son is now 15 years old and my daughter is 12. After the maternity leave, I returned to work at the University Children's Hospital, which has greatly expanded during the last decade.

Currently, this hospital (with 560 beds) is one of the largest multiprofile children's hospitals in Lithuania consisting of three clinics – surgery, paediatrics and neonatology. I work at a consulting department of the paediatric clinic, which has 200 beds and is to undergo a reconstruction.

There are five paediatric departments, an emergency department and a neurology department at the Paediatric clinic. Sick children with infectious diseases, gasrtroenterologic, cardioreumatologic, and nephrologic pathology are being treated here. Peritonial dialysis and haemodialysis are performed at the clinic and children are treated here after kidney transplantation. The clinic has the children's oncohaematology department, the only one of this kind in Lithuania. In 2002, a bone marrow transplantation division was established at the oncohaematology department and bone marrow transplantation for children started to be performed.

Since I work at a consulting department, my work is related to a very wide range of diseases. I have an opportunity to analyse many case histories of children from all over Lithuania. I meet many patients with very different abnormalities.

Once a year, I work at one of the hospital's departments where there is a possibility to go deeper into peculiarities of a narrower pathology. I have lately started to work additionally at the oncohaematology and paediatric departments as a paediatrician for providing medical service in urgent cases and this is how I have been confronted with problems of primary and secondary immunodeficiencies.

Can you give me some information about health care in your country?

Lithuania is the largest of the three Baltic countries (65,300 km2) with a population of 3,48 million inhabitants. Lithuania lies in Eastern Europe, on the coast of the Baltic Sea. In the north, Lithuania borders on Latvia, in the east and south on Byelorussia, in the south-west on Poland and on the Kaliningrad region of the Russian Federation.

The health-care sector in Lithuania has been under reform for seven years. In 1997, the payment system changed and from a state budgetary system we turned to a health insurance system. Primary health care is a priority of the health service, and a private sector is especially being promoted. It is common to create group practises from a few family physicians, a general surgeon, a gynaecologist and a psychiatrist. Only in small villages family physicians have their own practice.

The second task of reform was to reduce both the number of hospitals and the number of beds, because hospitals account so far for the largest share of the health budget (about 70 %). Restructuring

of the hospital system began 3 years ago. There are three levels of hospitals in Lithuania: - the third level, a university hospital, - the second level, general hospitals with acute beds, - the primary level, nursing (or geriatric) hospitals. There are two university hospitals in Lithuania: in Vilnius and Kaunas, and about fifty acute general hospitals and thirty nursing (or geriatric) hospitals. There are some special (profiled) hospitals in Lithuania, too (as for tuberculosis treatment, psychiatric, etc.) The private sector isn't popular in the country. There are only a few private hospitals based on foreign investments.

Restructuring of the hospital system means reducing the length of stay, improving and optimising clinical performance and achievement of the most effective and efficient treatment. While the primary health care and social care are not at a high level, hospitals must solve a lot of social problems.

Can you give me some information about PID-care in your country?

I am not able to give you much information about PID care in our country. Lithuania has not got a PID register or special service for patients with PID. Patients are treated in a number of different departments and often this type of pathology is hidden under other names of diseases.

There is a clinic of Pulmonology and Immunology in the Kaunas University of Medicine. They had some patients with CVID, selective IgA deficiency, 1 DiGeorge syndrome, Wiskott-Aldrich syndrome suspected, but I can't comment, because I haven't got the exact data.

Based on the information compiled by my teacher - immunologist assoc. prof. A. Rainyte and myself, I can state that within the recent decades in Lithuania the following diseases were diagnosed in children: 1 Wiskott-Aldrich syndrome, 2 DiGeorge syndromes, 1 Chediak-Higashi syndrome, 2 cases of ataxia-teleangiectasia, 1 chronic granulomatous disease, 4 severe combined immunodeficiencies due to thymus hypoplasia,5 congenital hypogamma globulinemia. However, most of pathologies were diagnosed clinically and were confirmed by Institute of Immunology in Moscow, London, Germany or following the patanatomy. Out of patients to whom congenital hypogammaglobulinemia had been diagnosed only one receives a continuous substitution therapy and lives a full-fledged life. In two patients, the disease developed into a bronchiectasis disease and in one patient it developed into Hodgkin's lymphoma. Wiskott-Aldrich syndrome was clinically diagnosed to a three-months-old boy, but confirmed in London at 2 years of age, and transplantation was performed at 5 and 6 in Poland. Presently, the patient is treated in Sweden against GVHD. During 2002-2003 two girls from one family died from a severe combined immunodeficiency.
So, it may be stated that PID cases exist in Lithuania, but this problem is not given a systematic analysis and therefore little is known about it.

How did you become interested in immunodeficiencies?

At first, my sphere of interest included infectious diseases and systemic vascular diseases in children. I yearly improved my qualification at the courses arranged by the Vilnius University and attended the Cornell seminars on infectious diseases (2002 update) organised by the American Austrian Foundation in Salzburg. I have also compiled data and written several articles on systemic vascular diseases such as Behcet's disease and Kawasaki disease.

In the spring of 2003, my teacher, immunologist assoc. prof. A. Rainyte, returning from the ESID conference in Prague suggested me applying for PID school arranged by ESID in Portugal. After receiving an invitation, I, in a very short time, tried to find out as much as possible

about this type of pathology. ESID School in Portugal became a great event in my life. There I understood how little we know in Lithuania about PID and what great achievements in this field have been reached in the world. Since then, my interest in PID is ever growing. I started compiling data about patients with suspected PID who had been treated at our hospital, attended a course of clinical immunology at the University and am preparing a presentation about a fatal outcome of two siblings with SCID and thymic hypoplasia for the ESID Prague Spring Meeting 2004.

What has been your role in PID-care in your country until now?

Since no special PID service has been established in our country, I have been engaged in this problem only on my own initiative.

What do you hope to achieve in the future?

I would like to learn more about PID, be able to help PID patients and implement an examination and treatment algorithm of these patients in our hospital.

After the establishment of children's bone marrow transplantation division in Lithuania, new opportunities to help such patients emerged. However, financial difficulties impede the implementation of these goals. Therefore, I would like to develop a project to draw our authorities' attention to this problem and enable Lithuania to be included into the PID registry developed by ESID.

How could ESID help to achieve this goal?

Due to differences of political and economic development, countries of the world have different quality of life, application of science to practice, but everywhere they do their best to seek progress and, due to this progress, the world has become a smaller place. Although economic development differs, diseases people suffer from are often the same. If it is a rare disease, medical people lack experience to diagnose and treat a disease in a single country. It is sometimes even considered that the problem does not exist at all. If you lack knowledge and information, you cannot systemise symptoms and may go the wrong direction. A doctor has no right to be so negligent and therefore must learn all his life. ESID is the organisation that provides an opportunity for medical people to learn and improve and a hope to a hopeless patient in your country of a cure to be discovered.

I am grateful ever so much to the ESID organisation for providing me with a possibility to attend the ESID Summer School and the knowledge I acquired there. However, in order to organise a wholesome help to PID patients and to join the ESID PID register, we urgently need further consulting and material assistance from ESID.

Rasa DUOBIENE
University Children's Hospital
Vilnius, Lithuania
(rasa_duobiene@yahoo.co.uk)

Online Registration

http://www.esid2004.org/registration.php

The XIth meeting of the European Society for Immunology (ESID) together with the **VIIIth meeting of the International P**
Organisation of Primary Immunodeficiencies (IPOPI) and the **VIth meeting of the International Nursing Group for**

Guidelines for submission of abstracts

http://www.esid2004.org/guidelines.php

CATEGORIES

1. T cell immunodeficiency

2. B cell immunodeficiency

3. Deficiencies of innate immunity (Phagocytic cells)

4. Deficiencies of innate immunity (Complement)

5. Stem cell therapy / gene therapy

6. Immoglobulin therapy

7. Genetics / genetic counseling

8. Quality of life

9. Other

ESID MEMBERSHIP FEE REPLY FORM ***Do NOT fax or email this form!!!***

Complete as soon as possible and send to: Dr. Esther de Vries, pediatric immunologist
Jeroen Bosch Ziekenhuis loc GZG
P.O. Box 90153
5200 ME `s-Hertogenbosch, The Netherlands

I wish to become a member / renew my membership of ESID for the years 2004 and 2005. If my membership fee is received before March 1, 2004, I will be entitled to visit the biennial congress in Versailles in 2004 for a reduced fee.

I will pay ☐ € 100 ☐ € 50 (Eastern Europe and/or < 35 years of age, please add proof)

I will pay by ☐ VISA ☐ AmericanExpress ☐ Eurocard/Mastercard

Name on card:……

Number of card:……Expiratory date…….

If you really cannot pay by credit card in any way (for instance through family, friends, colleagues), please contact me at esther_de_vries_nl @ yahoo.co.uk! Do NOT pay differently without contacting me, I will not be able to recognize your payment then, and you will not be a member!!

If the above mentioned name and address are not correct, please write the corrections on the reverse of this form.

Last name ……..…… First name …….

Place……..Country……Date……..

Signature……

Once I have received the money, I will sign this form as a proof of payment and send it back to you.

PROOF OF PAYMENT OF ESID MEMBERSHIP FEE 2004 / 2005

I have received € 100 / 50 as payment of the ESID membership fee 2004 /2005 from

……..

`s-Hertogenbosch, the Netherlands, ……..(date)

……..(signature)