

Twenty-five-years history of the Department of Immunology at the Children's Memorial Health Institute in Warsaw

EWA BERNATOWSKA

This year the Department of Immunology at the Children's Memorial Health Institute has been celebrating the twenty-fifth anniversary of the founding of the Department (Fig. 1). Since 1980 the Department of Immunology has been the reference centre for PID for the whole of Poland.

Patients: Every year more than four thousand suspected PID are admitted the Department.

Teaching: As a first teaching hospital in Poland, the Department of Immunology has been obtain accreditation to teach Clinical Immunology, as a specialisation in 2000. Specialisation in paediatrics has been provided for 20 years.

Education: It has been, a tradition for more than 20 years for the the Department of Immunology to provide numerous courses on primary immunodeficiencies, for both paediatricians and doctors specialising in clinical immunology.

Since 2002 periodic meetings have been organised in the School of Immunology. Young immunologists and doctors interested in clinical immunology from the whole of Europe are invited to spend time together (Fig. 2, 3, 6). The meetings give an opportunity to listen to lectures given by experts in immunology from all over Europe and the world. It also creates a forum to exchange their own experiences, as well as to discuss difficult cases and diagnostic and therapeutic problems.

We also organise regular educational and scientific meetings, at least once a year, dedicated to the National Programme of Vaccination as well as to adverse events following vaccination, particularly after BCG (Fig. 4, 5). Many Polish and foreign authorities take part in these meetings, creating changes in National Programme of Vaccination. It is worth saying that these activities has resulted in the position of country representative and adviser to WHO committees for Professor Ewa Bernatowska, head of Department of Immunology.



Fig. 1.





Fig. 2.



Fig. 3.

**Szczepienia
Ochronne**

Warszawa, 21 maj 2004



**Klinika Gastroenterologii, Hepatologii i Immunologii CZD
Polskie Towarzystwo Pediatryczne
Krajowy konsultant w dziedzinie pediatrii
Wojewódzki konsultant w dziedzinie pediatrii
Departament Profilaktyki Zdrowotnej, M.Z.**





Fig. 4.

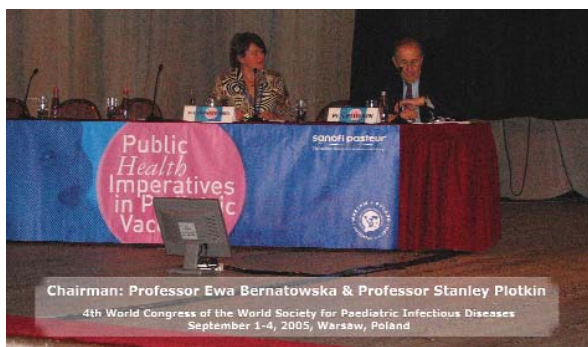


Fig. 5.



Fig. 6.

Publications: Three hundred and sixty five papers in a national and international journals.

Grants (recent years): Three grants within 6 Framework of EC project have been provided for the Department of Immunology:

- The Department has achieved the objectives of the PERFECT QLGI-CT-2002-90358 project, which has been provided by The Children's Memorial Health Institute as a Paediatric Research Centre – Focusing on Effective Child Treatment.

- EURO-PID-NAS QLGI-CT-2001-01395 as a first project focusing on the east/central Europe, forming the “Newly Associated States” at that time. This gave us an opportunity to spend up collaboration among European researchers (Fig. 7).

- EURO-POLICY-PID SP23-CT-2005-006411, a new EC project “Policy oriented and harmonized research activities in the field of primary immunodeficiency diseases” was initiated and co-ordinated by Professor C.I.Edvard Smith, Carolinska Institute, the leader of the EURO-PID-NAS project. The objectives of the new project are to build up necessary research capacity at the European level, in order to increase the understanding of PID etiology and identify novel mutations, to carry out epidemiological

studies in order to determine the prevalence of PID in Europe, to establish harmonized guidelines for diagnosis and treatment of PID, and to improve awareness of PID among the European population.

- The newly-accepted (by the Ministry of Science) national project PBZ-KBN-119/PO5/04, led by the Department of Immunology, with the aim of improving patient care in Poland and to raise awareness of PIDs across the country, was initiated by the Polish Working Group for PIDs (Fig. 8).

International collaboration: The Department of Immunology has been successfully collaborating with very well - known European and American immunological centres for diagnosis of PIDs. Within the past few years, the most fruitful collaboration in the field of molecular diagnostics, and genotype/phenotype correlation, was established with Professor Jacques J.J. van Dongen at the Department of Immunology, University Medical Centre Rotterdam.

Contribution: The Department is contributing to a variety of national and international scientific associations with a special focus on the Polish Paediatric Society, the Polish Society of Experimental and Clinical Immunology, and the European Society for Immunodeficiencies.



Fig. 7.



Fig. 8.



Fig. 9.



Fig. 10.



Fig. 11.



Fig. 12.

Patients

Primary Antibody Deficiencies: Antibody deficiencies comprise the largest group of PIDs, consisting of 547 patients. They result from inborn defects of the immune system, especially from B cell development. Due to cooperation with well-known European centres for immunogenetic studies in PIDs it was possible to include Polish patients into the programmes of molecular studies. In the field of molecular diagnosis of XLA we have been co-operating with Professor C.I.E. Smith from the Carolinska Institute and since 2000 with Professor Jacques J.M. van Dongen from Erasmus University. The national programme of substitutional replacement therapy was

initiated and conducted by our Department of Immunology in 1993. The programme and distribution of intravenous gammaglobulins to whole immunologic centres in Poland was financed to the early 2000's by the Ministry of Health, and now by the National Health Insurance system. The intravenous infusion of gammaglobulin has been provided for 20 years in the Outpatient Clinic of Immunology (Fig. 9). Due to rare adverse events in some patients, as well as to difficulties in vein access and the need for frequent hospital admission, these have been replaced by subcutaneous infusion (SCIG). The safety and easy infusion technique make SCIG a very suitable method for self-infusions at home (Fig. 10). Subcutaneous replacement immunoglobulin



Fig. 13.

therapy was introduced in our Department in 2001, for the first time in Poland, and has been continued successfully to date (Fig. 9).

Severe combined immunodeficiencies

The increasing knowledge of, and awareness about, the most severe types of PID has resulted in better and faster diagnosing of these diseases. In 1986 the first child with severe combined immunodeficiency was diagnosed in our department, followed by nine cases in the 90's and 19 cases between 2000 and 2006. The improvement in assessment of different lymphocyte subsets by flow cytometry plays a basic role in establishing the diagnosis, in parallel with determination of immunoglobulin, specific antibodies, and the proliferative response of lymphocytes to stimulation. Four-colour flow cytometry with a broad panel of antibodies allows us to bring the diagnosis to the stage of a targeted molecular background. Good examples are the common gamma chain, the IL-7 receptor α chain, adhesion molecules, and HLA class I and II expression. Since 2000, thanks to co-operation with Professor Jacques J.M van Dongen from Erasmus University in Rotterdam, molecular diagnosis is available for all patients with severe combined immunodeficiencies. A genetic defect was confirmed in 13 out of 19 investigated children. The final diagnosis confirmed at the molecular level is extremely important for further management of patients, particularly in making decisions about haematopoietic stem cell transplanting. It also makes prenatal diagnosis and genetic counselling possible for the family. Since 1997, when the first bone marrow transplant in an SCID patient was performed in the BMT Unit, Lower Silesian Center for Cellular Transplantation, Wroclaw by Professor Andrzej Lange, haematopoietic stem cell transplant (HSCT) has been an available method of PID correction in Poland. Eighteen SCID patients have been transplanted in three different



Fig. 14.

centres: in the BMT Unit, Lower Silesian Center for Cellular Transplantation, Wroclaw by Professor Lange, in the BMT Unit, Haematology and Paediatric Oncology Clinic, Children's University Hospital, Lublin by Professor Jerzy Kowalczyk, and in the Department of Haematology, Department of Paediatrics, Haematology, Onkology and BMT, Wroclaw Medical University led by Professor Alicja Chibicka. It has resulted in a good outcome in 15 of the children. The implementation of molecular techniques in diagnosing of some viral, bacterial and fungal infections, which is essential in regular monitoring and treatment of opportunistic infection (e.g. CMV, EBV, BCG, Aspergillus) in these patients has been provided in our hospital for many years. Successful therapy in most graft versus host disease (GvHD) after transplantation is performed in our department in cooperation with other specialists: pathologists, gastroenterologists and transplantation team. For the first time in Poland, liver transplanting by Professor Kaliciński, Department of Surgery and Transplantology from CMHI, in a child after HSCT was successfully performed in a boy with X-linked SCID. GvHD grade IV occurred after HSCT with skin, intestine and liver involvement (Fig. 11). Multidisciplinary care and intensive treatment have resulted in improvement of skin and bowel changes, but GvHD causes irreversible vanishing bile duct syndrome in the liver. In fact, the boy is in excellent clinical condition with full immunological reconstitution and good



Fig. 15.



Fig. 16.

liver function at a 3-year follow-up (Fig. 12). The experience of our department in management of SCID patients, presented during meetings and conferences for paediatricians, general practitioners and immunologists, is important in increasing awareness about these congenital defects, which we hope will influence faster diagnosing of these children.

Phagocytis defects: The Department has had the largest group of patients with chronic granulomatous disease (CGD). The genetic analyses were performed in co-operation with Professor Dirk Roos from the Department of Blood Cell Research, Sanquin Research, at CLB in Amsterdam. It is worth noting that some of them are unique and have not been previously described.



Fig. 17.

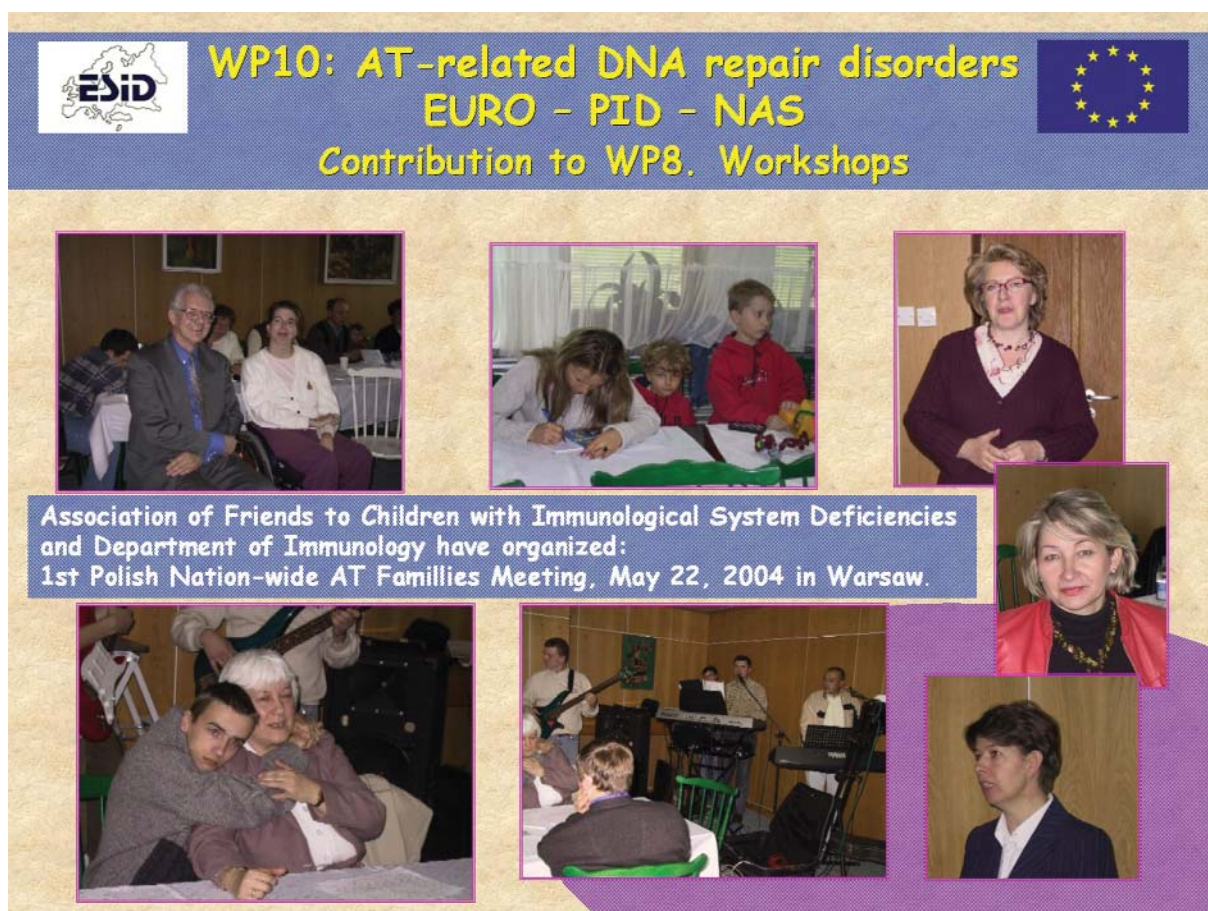


Fig. 18.

Following ESID recommendations, we have modified and implemented the diagnostic and therapeutic criteria for CGD patients. Twenty-five years of experience in therapy of fungal infections in these patients, especially of invasive Aspergillosis, has provided a good outcome due to multi-drug antifungal therapy, with a 40% survival rate (Fig. 13, 14).

DNA repair disorders: Combined immunodeficiencies associated with chromosomal instability were diagnosed in 152 children. Among them, the most frequent, ataxia-telangiectasia, was recognised in 92 cases, and second was Nijmegen Breakage Syndrome in 57 children. Bloom's syndrome was diagnosed in three children. This constitutes the largest group of patients with DNA repair disorders in the European registry. To improve the awareness of these diseases among general practitioners, paediatricians, and medical doctors in the Polish population, a brochure illustrating the most important signs of both diseases has been published (Fig. 15, 16).

Parents of children suffering from a serious disease feel very helpless, and if the disease is a rare one, like the syndrome of ataxia-telangiectasia, additionally often feel left alone with their problems. The Clinical Department of

Immunology at the Children's Memorial Health Institute and the Association of Friends of Children with Immunological System Deficiencies has organised twice, in 2004 and 2005, meetings for parents and their children affected by AT syndrome (Fig. 17, 18). The parents were really grateful for the opportunity to participate in the meeting. They realized that they were not alone with their problems, and that they had the possibility to learn more about their children's disease. At present the parents involved are establishing a Fund as well as their own website.

The Association of Friends of Children with Immunological System Deficiencies: The Association of Friends for Children with Immunological System Deficiencies was founded in 1987 thanks to the initiative of the Head of the Department of Immunology, Professor Ewa Bernatowska, together with parents of children treated in the Out-patient Clinic and Department of Immunology. The first leader of the Association was Joanna Zawadzka. Since 1999 Maria Bukaty has been managing the activity.

The main aim of setting up this unit has encompassed the support of children with primary immunodeficiencies and their parents. Basic activity comprises development of

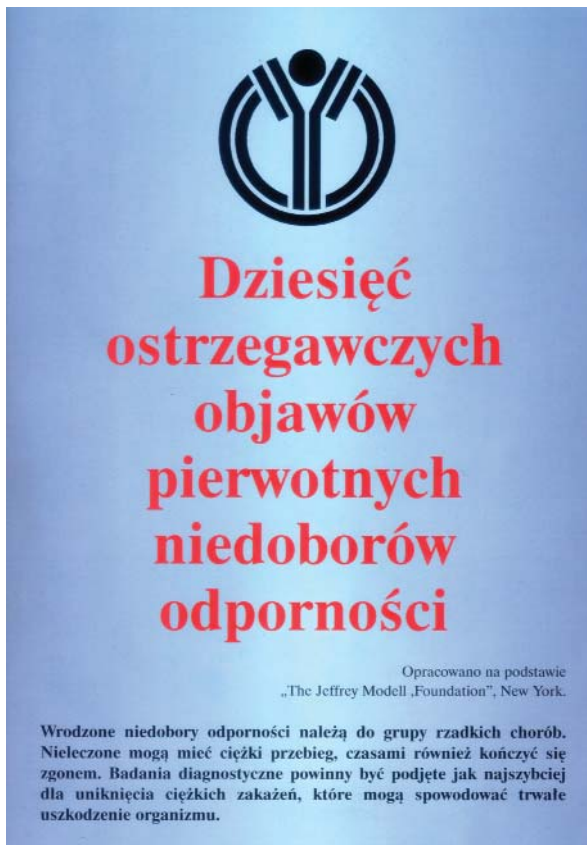


Fig. 19.

an educational programme for patients and families with primary immunodeficiencies, providing the children with exceptional or unique medicines, and information initiatives for doctors and parents concerning primary immunodeficiency disorders.

The Association was created on the basis of other supportive organizations in the world. The members originate from different walks of life: patients and their families and friends, doctors, nurses and other medical staff.

The Association co-operates with similar organizations such as ESID, IPOPI, INGID. Thanks to close partnership, the members of our Association are actively involved in participation in international conferences concerning primary immunodeficiencies knowledge.

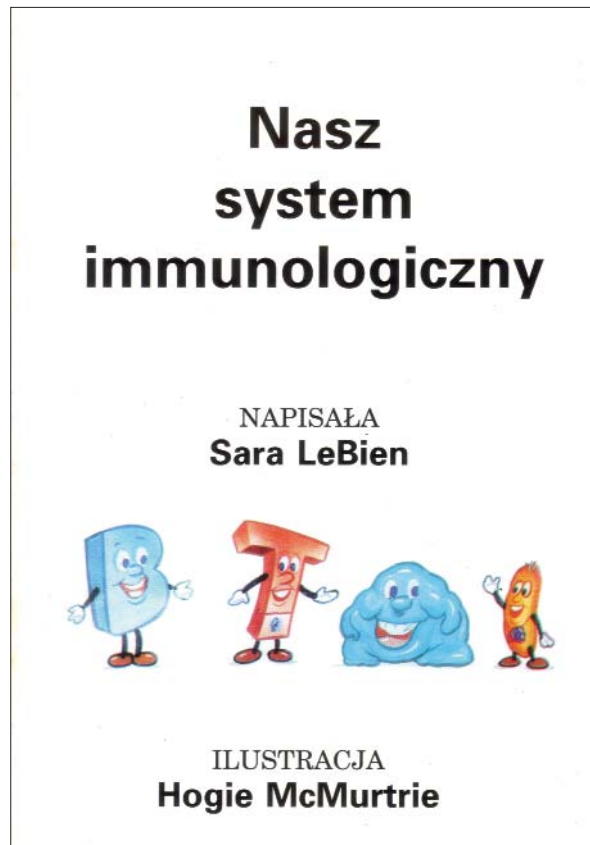


Fig. 20.

The Association has also published two brochures, "Our immunological system" and "Ten warning symptoms of Primary Immunodeficiency Disorders", which were aimed at doctors, patients, and their parents (Fig. 19, 20).

The future

The Department of Immunology at the Children's Memorial Institute in Warsaw is still developing, admitting more and more patients. At the same time, it is developing its diagnostic possibilities. Increased participation in research at home and abroad is still ongoing.