

An European educational programme on rare diseases

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Technical Report

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Description of the project

The project entitled "An European education programme for rare diseases" was intended to implement a number of public conferences with the aim: a. to improve the communication and co-operation among people professionally interested in rare disease in Europe; b. to offer occasions for the education and training of health professional and other interested persons, who are involved in the care of rare diseases (scientist, doctors, nurses, patient support groups).

Co-ordination of the project

The programme was co-ordinated by the Clinical Research Center for Rare Diseases of the Mario Negri Institute for Pharmacological Research. The Clinical Research Center for Rare Diseases is the site of an European School for Rare Disease which is specifically dedicated to implement training courses in Clinical Research for physicians, nurses, research technicians, statisticians, data managers. The activity of the European School is implemented through seminars, workshops, and courses that are regularly scheduled; meeting among physicians: and patients with specific rare diseases have been also held. The School has spaces for several type of reunions, from few people up to 200 people or more.

Partnership

The project is a combined effort of the following participants

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Activities

During the period of activity 3 conferences has been held.

Report of the Conferences

The role of patient support groups: social aspects of rare diseases

The First European Conference entitled "The role of patient support groups: social aspects of rare diseases" was held on November 8, 2002, in Ranica, Italy".

At the meeting were invited representative of the partners who have shared their experiences with an audience composed by people coming from Sweden, Spain, Italy, United Kingdom, France.

The first Euroconference entitled "The role of patient support groups for rare diseases" was held at the Clinical Research Center for Rare Disease, Ranica, Italy on November 8, 2002 (appendix 1).

The scope of the meeting was to bring together organisations of patient support groups and clinical research institutions, with the aim to find a common ground of discussion, collaboration, exchange of experiences. The final goals for all the actors in this scheme is to provide means for increasing the knowledge on rare diseases, seen from the prospective of their recognition, diagnosis, treatment and assistance. The strong believe of the partners in this Euroconference series is that only from a strong alliance between researchers and patient organisation can derive a new impulse in basic and clinical advancement. Indeed, public health authorities and those bodies entitled to provide funding for research, are increasingly attentive to the keywords of rare diseases, but it is of paramount importance that citizens and scientists show their common interests in the advancement of research.

The meeting was opened by a presentation of Dr. Arrigo Schieppati of the Mario Negri Institute, of Italy, who has illustrated the activities of the Institute.

The Mario Negri Institute for Pharmacological Research is a non-profit foundation, which was established in 1963 in Milan to study human diseases, with particular emphasis on the mechanism of action of drugs. The Mario Negri Institute has three campuses in Italy, and in 1992 it has established the Clinical Research Center for Rare Diseases "Aldo e Cele Daccò" in Bergamo.

This facility has no comparison in Italy and perhaps in Europe, since it is the first example of a research facilities entirely devoted to all the aspects of rare disease care, in which research, information and education are strictly intertwined-

The programs of the CRC are

Clinical research on rare diseases, with special regard to the development of innovative therapeutic approaches

Information to the patients; collaboration with patient support groups and local and national health authorities to improve assistance and care of patients with rare diseases

Teaching and training for all those professionals involved at different levels with rare disease patients.

These three lines of action are put in practice in the Center's facilities which are organised as following:

The Clinical Research Center: it is a fully equipped and staffed clinical facility for admission of inpatients and for the follow up of ambulatory patients, which are involved in clinical projects on given rare diseases. The Clinical Center take advantage from the availability of expert personnel who provide such services as data entry and analysis, and study monitoring.

2. The Information service: It is basically a service to the public and its aimed to provide up-to-date information on rare diseases with particular emphasis on aetiology, pathogenesis, genetic aspects, preventive measures, established and experimental

treatments, referral research centers. The Information Center for Rare Diseases is directed by a medical doctor who co-ordinates the activities; the staff is also composed by two full-time doctors, two registered nurses, part-time consultants in different sub-specialities of medicine. By November 2002 the Information Center has provided written information to more than 10 000 patients, relatives or physicians. About 75% of the requests concerned rare or orphan conditions; 17 % of applicants referred not yet diagnosed condition; the remaining patients had common clinical conditions, characterised in the majority of cases by severe or irreversible course. More than 900 different rare or orphan diseases were classified; for each of these conditions a 5- to 10-year bibliography search has been performed and a relevant number of up-to-date published reviews has been collected.

3. The European School of Rare Diseases. The Mario Negri Institute - beside its research activity - has a long standing tradition in education and cultural promotion in the field of biomedicine and human health. The Center will be the site of an active cultural activity on several levels, which will be aimed to both specialists and training health professionals. Regular courses for training in clinical research are already implemented for medical doctors, registered nurses, and statistician. Workshops and conferences are regularly scheduled all over the year. Meetings between doctors and patients with rare diseases are also frequently held.

During the last years the Clinical Research Center for Rare Diseases has grown to become a reference point for rare disease in Italy, and has significantly contributed to the shaping of provisions in favour of the patients with rare diseases, which were first introduced by a Government act in 1998, and which are now in the process to be implemented.

Finally, the presentation have briefly illustrated some of clinical studies currently taking place at the Clinical Research Center, which are generated by the unique opportunity to have clinical research facilities in a center that is also a clearinghouse for patient information.

Dr. Anders Olauson, of the Agrenska Foundation of Sweden has then illustrated the activities of his institution, and in general the activities in favour of patients with rare diseases in Scandinavia.

The Agrenska actions are mostly centred on the relationship with families. During the last decade (1990-2001), more than 2000 families including nearly 2400 diseased children and 2500 siblings, had visited Agrenska. More than 160 rare diagnoses has been recorded. The advantages of such activities are the following:

Parents feel "normal" for the first time

The family feel empowered, by meeting other in the same situation

Parents get new knowledge, to take better care of their own life

Children with the disorder meet other in the same situation

Siblings meet other siblings

The value of sharing the experience with other that understand, to meet possibilities rather than problems and to contact with different authority's is one of the most important element in Agrenska experience for most families.

Dr. Olauson have particularly focused his attention on the problem concerning the family around the children with rare disabilities. He confronted the expectations of patients with common and rare diseases. For common diseases, progress has been made : there has been advances in scientific knowledge and medical care, better access to information, better access to medical files and new treatments, involvement of patient/consumer organisations in their own health problems, participation of patients in clinical trials protocols. Moreover, although there is still

no cure for many common diseases (cancer, cardio-vascular..), industry is spending money on research and new treatments. As for rare diseases: Great number of diseases (+5000) but small number of patients per disease (5/10000 in EU, 1/10000 in Sweden), for many years there was no understanding nor knowledge of these diseases. Often no treatment available, no cure is available, and most of them are ORPHANS, too narrow market for Industry. But patients expectations are the same as in other diseases: patients need safe and efficient treatments, patients need a cure. Indeed the patients needs are the same either their disease is common or rare:

- Understand their disease and why they are sick
- Appropriate treatments : safe, efficient, good quality drugs
- Good and clear Information on this treatment
- Cure as soon as possible
-

In Dr. Olauson opinion, many patients or patient organisations are not waiting but are actors in their own health care and treatments. They promote research and scientific advances in their disease, identify bottlenecks, fill the gaps, provide resources for innovative projects, lobby for new legislation. In rare diseases, patient organisations are well known to be very active partners and provide information

At European Union level, patients are involved in European public health policy, health Forum, COMP.

In this context the strategy of AGRENSKA is aimed to increase knowledge for the patients and closest relations; decrease insufficient contacts with different institutions; more correct activity's from different institutions e.g. Hospital, school, social services etc.; adapt the latest medical knowledge to other areas, e.g.

Pedagogical implications. In the future the goal is to develop the knowledge and tools for research in genetics, gene therapy, biology; to give birth to the concept of gene therapy and prove feasibility of this concept.

Dr. Olauson in his talk has also briefly reported the experiences of other organisations in Scandinavia such as Institutt for sjeldne diagnoser, National Resource Centre for AD/HD, Tourette Syndrome, Norske Forening for Cystisk Fibrose, Frambu National Information Centre for rare disorders and disabilities, in Norway; Center for SMA Handicappgrupper, De Samvirkende Invalideorganisation in Denmark; the STAKE initiative of the Finnish Government.

The experience of Spain has been reported by members of the FEDER, Federación Española de Enfermedades Raras. (drs. Rosa Sanchez de Vega)

FEDER s birth was in April 1999 after a meeting in Sevilla, October 1998 which served to study the situation of patients with rare disorder. It was convened that the problems of patients wit rare diseases are isolation, lack of support, information, treatment and research. In Spain the Associations were weak, with few members.

There was the need to speak with one voice at national level and European level

These are the Feder´ s goals: Recognition of Rare Disorders as a public health problem; improve information, social and health assistance; promote research and development of new therapies; defend affected people's rights

Feder´ s has greatly developed: in 1999 there was no social site, personal staff, office equipment financial support

Difficulties of awareness: 7 members only

In 2002 there is the social site in Sevilla and there are 4 branches, with social workers, computer facilities, there is some financial support and there 53 member associations. Financial support is provided by Public Institutions, such as Ministry of Health, and by Private Institutions, such as Fund La Caixa, Obra Social. Caja Madrid, Fund Inocente Inocente.

The role of FEDER is

Contact people with RD

Gather and give information: health, legal, social aids

Offer social and psychological support

Promote and collaborate research

Make professionals, industry, administration and, society aware of public deficiencies when possible.

Feder's activities and future projects are concentrated on information, with the establishment of a Help line, the publication of a newsletter "Papeles de FEDER", and the launch of a Web site: www.minoritarias.org. FEDER is also very active in seeking collaboration with Spanish Organisms, such as CISATER-Centro de Investigacion sobre el Sindrome del Aceite Toxico y Enfermedades Raras, for the Web site, the study of diagnosis delay, the creation of the data base; Barcelona University for the study of therapeutic needs of patients; with the Ministry of. Social Services, to establish a National Plan of Action on rare disease; with the Spanish Ministry of Health for establishing a National Institute of Rare Disease.

FEDER, finally has established collaboration with European Organisms: EURORDIS, Eurobiobank, Eurordiscare, EMEA-COMP, Epposi and Mario Negri Institute.

The last talk of the day was given by dr. Sessa of UNIAMO. UNIAMO was founded in Rome in 1999, as the first and only Italian Rare Diseases Federation. Uniamo's aims are to defend the rights of persons afflicted by a rare disease: treatment, access to medicines, laws, besides increasing public awareness through meetings, newspapers, television and radio. The philosophy of UNIAMO is to think globally ...

To help: The Institutions to put into practice the right answers to patients' needs

To spread: The need of research not only medical, genetic and scientific, but even psychological and social for improving the quality of life of all people affected by rare diseases

To promote: The idea of a Society more aware of disabled rights and of the integration of diversity.

To support: The importance of a well balanced attitude far from culture of scientific omnipotence and from the wish of magic solutions.

... but to act locally:

To help: The families on the way of acceptance and treatment of the son

To spread: The specific knowledge on particular pathology

To ensure: The availability and the access to medicines

To promote: The study of clinical protocols and of nursing networks for an effective undertaking of a global and social integration

To assert: The right of live a life with diversity/disease

The Bylaws of UNIAMO, also called MAGNA CHARTA

PRINCIPLE OF NOT EXCLUSION: The rare diseases Associations have to be invited to participate to all the study round tables: regional, interregional, national since they are the keepers of experience and culture.

PRINCIPLE OF SCIENTIFIC UPGRADING: Many Associations support clinic and genetic researches: the results can be standards even to the other pathologies. The documented scientific effectiveness must be available for everyone and must be supported by institutional funds.

PRINCIPLE OF ETHIC AND TRANSPARENCY: Every Association has to guarantee levels of ethic and transparency in each action they take part. Moreover everything must be in synergy with the other Associations.

PRINCIPLE OF TRAINING: The Associations have to participate, together with the scientific societies, to the working out of sanitary education programs for the training of medical and paramedical staff in order to improve the assistance and the nursing of the persons affected by rare diseases.

PRINCIPLE OF SAFEGUARD OF THE DIVERSITY: The Associations have as primary task to mind for the partners providing them a good quality of life in accordance with the different disease. Every diagnostic-therapeutic action has to be finalised to improve the quality of life.

PRINCIPLE OF RIGHT TO HEALTH: The Associations have to apply themselves to guarantee the application of the right to health sanctioned by the Constitution ensuring the same preventive, diagnostic, rehabilitative, curative opportunities.

PRINCIPLE OF APPLICATION: The Associations constitute themselves as a "permanent observatory" to verify the application of legislative actions of the European, national and regional Community.

At the end of the presentation a discussion of the talks was chaired by dr. Moises Abascal and Maravilla Izquierdo Martinez.

“Methodological Aspects of Clinical Trials in Rare Disease”

In a recent issue of the *New England Journal of Medicine*, the results of a clinical trial of itraconazole for the prevention of severe fungal infection in children and adults with a rare condition, chronic granulomatous disease, were reported. This trial required 10 years to enrol just 39 patients. The study illustrates some of the problems and options that arise in the design of clinical trials of new therapies for rare diseases.

The issue is very important, and was chosen as topic for the Second Conference of the European Educational Programme on Rare Disease, which was held in Ranica-Bergamo, Italy on July 10, 2003, entitled “Methodological Aspects of Clinical Trials in Rare Disease”. The conference was assisted by a large audience from several European countries. The program is enclosed (appendix 2).

After a short introduction by Arrigo Schieppati, the first speaker, **Dr. Brendan M. Buckley**, from the European Center for Clinical Trial in Rare Disease, University College of Cork, Ireland, spoke on the following topic: “Clinical Trials: The Gold Standard”. Dr. Buckley firstly discussed how the methodology of clinical trials has taken place in modern medicine, and summarised which are the main characteristic of this methodology.

A clinical trial protocol has to pass through a number of steps, from design to ethic committee or IRB approval, from recruitment of patients to monitoring and data collections, as fast as possible and at the lowest cost as possible. As stated by Furberg, trials must be capable of being generalised to broad elements of the population of patients at large. Clinical trials are developed along a series of step that highly standardised, which are termed as Phase, from I to IV. The phases are

pretty linear when we are dealing with common conditions. However, for rare diseases may not be so. Also from the legislative point of view, rare diseases are considered differently, since a specific law is in force in Europe to promote development of medicinal products specifically dedicated to rare diseases, the orphan drugs. Dr. Buckley has then gone into the details of the process that is required under the Orphan Medicinal Product Law in Europe, for Orphan designation and the market authorisation.

Then Dr. Buckley has developed an analysis on the most used methodology for the evaluation of results of clinical studies, the frequentist analytical method. This method can be applied to rare disease with more difficulty than in common conditions, unless the effect of a new treatment is very big. For instance, treatment of Gaucher disease with Aglucerase is so effective in improving the clinical conditions of the patients, that studies employing frequentist analysis may be applicable. However, other designs are needed in other conditions, for which such so effective treatment are not available., Also a very important issue in rare disease is the problem of placebo in clinical studies.

The second speaker was **Dr. Antoine Flahault**, of the Inserm Unit 444, University Pierre and Marie Curie, Paris, France.

He discussed the practical limitations of classical methodologies in small populations. What is a small population in randomised clinical trial (RCT) ? A population may be defined as small when a trial of sufficient size to provide an appropriate answer is practically impossible to conduct because of difficulty of recruiting sufficient patients. Which are the consequences of a RCT of sufficient size in small populations? Such a RCT would need to recruit from very large areas, over long periods of time, resulting in a expensive, difficult to realise, then not undertaken,

trial. Funding, sponsor's acceptance, ethic committee approval, publications are very difficult to obtain for RCT of treatments showing worthwhile effects that have little chance of producing a result at classic levels of significance.

After examining all the aspects of current practice in clinical trial design and implementation, underlining the critical problems emerging when such methodology is extended to the rare disease, a number of final proposal has been discussed by Pr.Flahault.

Non-standard techniques, such as Bayesian approach, early stopping rules, sample size adjustment may save an average of 30% of the planned recruitment.

Non randomised designs, although less reliable than RCT may be of valuable contribution, particularly if they assess clinical endpoints.

Cohorts, case-control, and case-crossover designs are better than case series and experts' opinions.

Record linkage should be more developed in Europe.

New designs (e.g. case-crossover) should be better experienced by regulatory agencies.

RCT must be adapted for small populations.

RCT should not be rejected if appropriate standard calculation of sample size is not provided, since non biased information may be re-usable

Meta-analyses should be promoted.

Alternative statistical approaches should not be rejected. Compliance and contamination must be carefully monitored during these trials.

Drs. Guido Bertolini and Davide Luciani, Laboratory of Clinical Epidemiology, Mario Negri Institute, developed in their talk some issues on the subject of "Bayesian methods" in clinical research. They underlined that the Bayesian method (BM) differs from the frequentist approach (FA) from a philosophical point of view, in that FA

states that there exists the Truth, which should be the goal of human knowledge it is not possible to eliminate serendipity from human knowledge, the goal of which should be the treatment of uncertainty. The differences are marked as far as the inferential approach: the FA says that inference regards the data as random and the efficacy as fixed (even though the data are known and the parameter is unknown) inference regards the update of uncertainty, given the data gained. The FA aims to significantly approach the absolute knowledge, and then to behave consequently, BM aims to take the decision that maximises the probability of the expected utility. These very different approach to clinical research had been then illustrated by theoretical examples, with sophisticated mathematical approach.

Dr. Annalisa Perna, head of the Statistical Laboratory of the Dept. of Renal Medicine, Clinical Research Center for Rare Disease, Ranica-Bergamo, Italy, presented the last talk of the day, entitled "Quality of published randomised controlled trials in rare disease". This is an original approach since applied the techniques of the Cochrane collaboration and of the meta-analysis to the analysis of clinical studies in rare disease. The aim was to investigate which procedure were used to analyse the data, if usual recommendation were followed, or novel approaches adopted.

A group of 50 rare diseases were selected from the Registry of the Information Center on Rare Diseases of the Mario Negri Institute. In this sample of RD, there were conditions of genetic or acquired nature; all medical specialities were included. Of the 50 initial selection, in only 27 diseases at least one RCT had been conducted; then only 18 diseases remained after the RCT, examined according to the criteria of the Cochrane collaboration, were felt eligible for analysis.

Such analysis, which is reported in details in the enclosed set of slide print-out, showed that a number of methodological problems are present in the published RCT in rare diseases. In particular, issues such as the power of the studies, the time of

patients recruitment, the use of the placebo or control group, are only few example showing that methodological problems are to be resolved.

In conclusion:

Whenever feasible, RCTs in rare diseases should be performed with the highest standards. Weak points found in RCTs on common diseases become issues of great concern in rare diseases.

When applicable, novel approaches should be better implemented, particularly when focused on saving the number of patients enrolled.

Prospectively designed extension studies after trial completion should be planned in order to assess long-term efficacy and safety of the treatment

Prospectively designed meta-analyses should be considered in order to standardise methodology and to increase the power of analyses.

“Having a Child with Rare Disorder: Implication within the Family”.

The Agrenska Academy, as partner and in the frame of the European Educational Programme on Rare Disease, has organised a two-day conference on October 21-22, in Hovas, Sweden, where the Academy has its site, entitled “Having a Child with Rare Disorder: Implication within the Family”.

The aim of the conference was, beside bringing together people with rare disorders, their families and different professionals, also to stimulate new projects as a result of the discussions held during the two-day conference.

There are many parents throughout Europe today who share the same experience and knowledge about what happens in a family when their new-born child is affected by a rare disorder. It does not matter where they live in Europe -this knowledge concerns all families. The problems occur when people on which they and their children depend, don't share or understand their experience. During the two-day conference the speakers has presented a perspective on all important aspects of having a child with a rare disorder. Many experts of the field have presented their latest research, related to children with rare disorders, and a strong family perspective has been given to all topics at the conference, in order to enhance understanding among all involved persons.

The conference, which was attended by no less than 100 people coming from 9 European countries, USA and Egypt, has been made available through a live webcast to all those interested world-wide, thanks to the collaboration of Microsoft. The live internet conference has been considered an opportunity to raise awareness of rare disorders among a global audience who share common concerns, and offered the

opportunity to everyone who was not able to come to the conference to assist to it.

The speeches have been registered and are available to everyone at the Agrenska site, at the following address

http://www.microsoft.com/sverige/giving/agrenska_konferens.asp

The conference has been opened by Dr. **Anders Olauson**, director of the Agrenska Academy. Dr. Olauson had the and the privilege to introduce **Her Majesty the Queen Silvia of Sweden**, who honoured the Conference with Her presence, addressing the audience with words of encouragement and praise for the efforts that in their different Institution in Sweden and in Europe are brought about in favour of children with rare diseases and their families. It has been a very important and touching moment for all the participants, who will keep the memory of this day.

After the opening ceremony, **MRS. BERIT ANDNOR**, Minister for Children and Families, from the Department of Social Affairs in Sweden, presented the Swedish approach. Mrs. Andnor has stressed the concept that in a modern society a policy in favour of disabilities is a matter of democracy, reminding the United Nation convention on children's right as a milestone. She has also underlined the priorities for the Governments of the European Union such as prevention, the support for parents in need, the mobilisation of special resources and expertise. In her conclusion Mrs. Andnor has not failed to mention the importance of the patient support groups.

This topic has been at center of the presentation of **Terkel Anderson**, Denmark, President of Eurordis, the European federation of patient support groups. Dr Anderson has underlined the odyssey of patients and parents in the quest of diagnosis. Reporting the results of surveys conducted by the organisation, that demonstrate how can be intolerably long the delay from the first clinical symptoms to confirmatory diagnosis, and how - for the same disease - the time can significantly

different in different countries, a signal of inequality in the quality of care of rare disease in Europe. The inequalities are also reflected by the variability in the availability of orphan medicinal products in the EU countries, even though these products have all been approved by the EMEA. Also the price differs widely among countries. The survey conducted by Eurordis also stressed the difference among European countries in term of rate of social expenditure on disabilities; in term of availability of support services for disabled pupils in the public schools; in term of public attitudes to people with disabilities. Terkel has finally stressed the role of patient support groups, showing an interesting data: patients with diseases that have a support group since longer time, are more likely to obtain social services and reimbursement for their condition.

The family perspective on rare disorders has been then offered by a number of presentation mostly from Sweden, by **Elisabeth Wallenius**, of Sällsynta Diagnoser, **Carina Hvalstedt**, of Ågrenska, **Lotta Dellve**, of the Gothenburg University and **Jan Andersson-Norinder**, Mun-H-Center Orofacial Center in Sweden. The topics covered by these lectures included issues related to different problems that are encountered by patients and families when there is a chronic disease that afflict the person from birth to adult life, changing every time its burden; the different reaction to a patient condition by mothers and fathers and siblings. It is worth mention here among this set of presentations, the report by Anderson-Norinder on the activities of Mun-H-Center, the national referral center in Sweden for oro-facial problems in patients with rare disorders. The Center, located in Agrenska - Gotheborg, is supported by the national government, and is a meeting place for patients, relatives, health professional and organisations. The oro-facial problems in several rare disorders are associated with severe deficits in vital function such as communication and nutrition, and the aim of a better quality of oral health is very important for many children. A

survey on 1262 patients has shown that 40% had eating difficulties, 52% speech problems, 28% drooling, and 7% bad oral health. The solution of oro-facial problems of disabled children requires a multi professional co-operation, and a true oro-facial health team. Mun-H aims to spread the knowledge and the experience gathered, with the purpose to assure early identification of the problems and improve preventive oral care. Very interesting are the oral motor therapy instruments, that have been developed as special toy kits that children are happy to use.

Lotte Delve, of Agrenska, has illustrated some of the research projects of the Center, conducted in collaboration with the Nordic School of Public Health and the University of Gotheborg. The object of one of such studies was the evaluation of stress experienced by mother who have children with rare disorders. One hundred and forty families have been involved and studied with a number of evaluation scales apt to measure parental stress, self-evaluated health status, social support etc. The study has demonstrated how the stress strain is particularly heavy on the mothers, and how it can compromise their health status. The families were then involved in family programs based on competence and empowerment, and re-evaluated at 6 and 12 months. The results show that the programs were associated decreased stress for father, and decreased strain for full-time working parents. Mothers experienced an improve health status, felt more supported by the spouse, and thought to have more competence to handle every day issues related to children disabilities. Interestingly, this study has shown also that different type of disability (behavioural, physical, deviant, or progressive) are associated with different kind or degree of parental stress.

Then a set of three presentation has brought the view of the problems from an international perspective. **James Hanson**, of the National Institute of Child Health and Human Development, a branch of the National Institute of Health, Bethesda,

USA, has illustrated the goals of his Institute, which can be broadly defined as the will to translate science into better care, treatment and prevention of rare diseases of the children. The NICHD is organised in a number of branches. Among them a particular emphasis is posed on the problems of mentally retardation, development disabilities, of pregnancy and perinatology. An important branch is dedicated to studies on developmental biology, genetics and teratology. The CDBPM, composed of the Office of the Director and three branches, serves as a major National Institutes of Health (NIH) source of support for research and research training in maternal, foetal, and infant health, and disorders of human development. Through research funded under grants, contracts, and co-operative agreements, CDBPM-supported scientists are advancing fundamental and clinical knowledge about maternal health and problems of child development, such as preterm birth, mental retardation and developmental disabilities, congenital and genetic disorders, foetal growth restriction, and other conditions. The Center and its programs are helping to maximise human development, prevent diseases and disorders, and improve diagnoses, therapy, and clinical care. The major goals of the Center are to promote the health of mothers and families, and to ensure that all babies are born healthy and are able to achieve their full potential, free of disease or disability. Areas of interest include autism research center, birth defects fragile X syndrome, muscular dystrophy.

Stephen Groft, Director of the Office of Rare Disease, another branch of National Institute of Health, then illustrated the activities of the ORD. The budget of this office has been of \$11.172 millions. Its responsibilities are the recommendation of research and public education priorities for NIH, the promotion, co-ordination and collaboration on rare disease activities between the NIH and extramural institution. Also important duty of ORD is the organisation of an information center, responsive to the public, medical professionals, patients, families.

The ORD has an internet site, <http://rarediseases.info.nih.gov/> that counts thousands of contacts every year. At this site are available a different sort of information, including information of grant applications. An important part of ORD activities is the organisation of scientific conferences, aimed to different aspects of rare disease research and assistance. During the last year a vast program called Cooperative Rare Disease Clinical Research Network has been launched with the aim to facilitate clinical research in rare diseases, training of clinical investigators. In particular, longitudinal studies on rare disease patients, and clinical pilot or demonstration projects are encouraged. At the present time the following conditions have been selected for the first Clinical Research Networks: defects in steroidogenesis, idiopathic bone marrow failure conditions, inflammatory vasculitis, nervous system channelopathies, urea cycle disorders, lung disease, Angelman Syndrome, Rett Syndrome, Prader-Willi Syndrome.

In the future, ORD aims to establish a National Rare Disease Patient Registry, besides continuing its role in supporting training programs and information services to the public.

The experience of the Clinical Research Center of Rare Disease in Bergamo, Italy, has been illustrated by **Arrigo Schieppati**. The Center has been established in 1992 by the Mario Negri Institute, a private foundation dedicated to the biomedical research. The mission of the Center is to develop research projects with special emphasis on rare disease and orphan drugs. The Center is articulated in three section, that include: the Clinical Reserch Center (a fully equipped hospital for patient admission); an European School of Rare Disease (a facility for meetings and conferences, and a permanent educational program for doctors and nurses) ; an Information Center. The latter is a free-of-charge information service that has helped more than 10,000 people in the last ten years, providing any sort of information on rare diseases. The Center has played an important part in shaping the

Italian legislation in favour of rare disease patients. The Center being part of a research Institution, the Mario Negri where most of the research projects are basic science-oriented, is a natural laboratory for the translation of basic research results into clinical practice.

The following day first lecture was given by Mrs. Leslie Green, from UK. Mrs. Green is Regional and Development Manager of CLIMB, Children Living with Inherited Metabolic Diseases. The foundation was established in 1981, and first supported cystinosis. Then it widened its range of interests and it is now representing some 700 metabolic diseases. Climb is committed to fighting metabolic diseases through research, awareness and support. They are the UK's only dedicated organisation to provide advice, information and support on all metabolic diseases to children, young adults, families, carers and professionals. There are over 16,000 families affected by Metabolic Diseases in the UK over 35,000 throughout Europe and over 65,000 in the USA. Scientists throughout the world are very focused on discovering the causes of metabolic diseases, how they can be prevented and how current methods of diagnosis and treatment can be improved. The extremely vital work costs millions every year. The research work that Climb funds is proactive, meaningful and occasionally fruitful. Climb is a national organisation working on behalf of children, young people, families, carers and support groups affected by metabolic diseases (genetic disorders). CLIMB has put particular emphasis on assuring the changing needs of a child with rare disease are met while growing. Indeed, families are confronted with different problem, from any point of view - medical, educational, psychological - when a child becomes an adolescent and then a young adult. CLIMB staff puts a special effort to understand and support every need.

The three last speeches of the conference, given by **Christopher Gillberg** of Gothenburg University, **William Gunnarson** of Orphan Europe, and **Stefan Johansson** of Funka, Sweeden, have all underlined the need of a new perspective. The need to

consider the problems of childhood beyond the age of childhood, the need to establish broader co-operation among different professions and expertise, but also across the borders in a truly effective international Cupertino, the need to give to socio-economic facts the due importance and acting consequently in political terms, all this questions have been raised and offered to the thoughts of the audience.

Appendix: Results of the Conference

1. The role of patient support groups: social aspects of rare diseases

COMMENT: this conference was aimed to bring together patient associations and researchers with the aim to present their different points of view on several subjects of relevant interest for patients with rare diseases.

The mission of the basic and clinical researchers in its true essence is not different from that of patient support group: promote the knowledge aimed to improve the diagnosis and the treatment of diseases, offer the best available information to the patient and his/her family in order to allow them to cope with the disease with lowest possible degree of suffering. Of course patient and scientist pursue their scope through very different ways, but they are natural allies. This seems to be too obvious, but it is not so. Sometimes researchers are concerned with their projects, and increasingly involved in administrative duties that may distract them from a sincere contact with the public. Patient advocates are often more concerned - at least in some countries - to deal with social aspects of the burden of the disease and are less concerned with the research advances, and in some way trust with not much criticism science as a response to their needs. In the relation between these two actors should also remembered the role of third parties, such as the health authority and the health industry. In summary, the conference has put at the center of discussion the interaction between academic institution and patient associations, and the definition of role of patient associations in participating and promoting research projects. If a conclusion can be drawn, it has been stated by all parties that a new strategic alliance between the researcher and the patients should be pursued. The attendance was composed by physicians, nurses, psychologists, statisticians, other health professionals and a significant number of patient associations representative.

2. Methodological Aspects of Clinical Trials in Rare Disease

COMMENT: the conference has underlined the need to investigate into new methodologies to study rare diseases. These conditions are often called the health orphans: there is little knowledge about a great number of them, there has been lack of sufficient funding to study them for a long time (and still is probably lower than needed); there is a lack of suitable animal models; and finally the interest to develop new medicinal product to treat rare diseases is low, because of scarce commercial appeal of drugs for a small group of patients. One of the difficulties encountered in developing new medicinal products for rare disease patients is intrinsic with the definition of rare disease: few patients have that disease, they are difficult to locate, they are spread over a vast area, it is difficult to select a cohort of patients with uniform characteristics. The classical statistical approach is therefore not always applicable to study rare diseases. This is reflected by the uneven quality of published studies in small population of patients.

3. Having a Child with Rare Disorder: Implication within the Family

COMMENTS: As underlined by the closing remarks of Anders Olauson, the conference has provided the opportunity to examine the multiple implications to the chronic disability that most rare diseases are imposing to the families, and to the communities at large. The conference has brought together people with very different backgrounds and personal expertise: basic science and clinical researchers, social workers, educators, healthcare authorities, politicians, patient representatives either as family members or support groups. This really depicted the broad range of attention and interest that is growing in our societies in Europe on the needs of patients with rare disorders, although it also underlined that the occasions to gather such a variagate range of expertise is not frequent enough. The conference was

therefore seen as a perspective for the future, that projects beyond the today the commitment to work for the needs of children and parents. It was very important to obtain the attention of political authorities because a strong political commitment is indispensable to work for a just society, open to the needs of the sufferers. The presence of people from the scientific community and the pharmaceutical industry has supported the notion that emerging technologies, such medical genetics, are changing the way we look at the diseases, without forgetting that we have to deal with people with a multiple level of needs.

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