

## VII INTERNATIONAL SYMPOSIUM:

### **EARLY INTERVENTION IN DOWN SYNDROME AND OTHER DEVELOPMENTAL DISABILITIES**

#### Theoretical Bases, Research and Clinical Implications

#### **ABSTRACT**

Title of conference: What is Early Intervention and why apply it?

Professor: Dr. Juan Perera. Director of the Príncipe de Asturias Centre. University of the Balearic Islands (UIB). Mallorca. Spain.

#### **TEXT:**

This first paper of the SYMPOSIUM will take Down Syndrome (D.S.) as a paradigm for intellectual disability of genetic origin, and EARLY INTERVENTION (EI) will be presented as the most effective treatment for reducing, and as far as possible, eliminating, delays in the ontogenetic development of people with intellectual disabilities.

A systematic model of EI will be defined and defended, based on a multi-disciplinary approach and on experiences; and emphasis will be placed on its preventive role, as highlighted in Spain in the new "*Ley de promoción de la autonomía personal y atención a las personas en situación de Dependencia*" or "Law on the Promotion of Personal Autonomy and Care for People in a Situation of Dependency" (*Law 39/2006*)

EI's short-term effectiveness has been sufficiently well demonstrated, but there are methodological obstacles in demonstrating its long-term effectiveness. So, EI faces important challenges: better specification of children and family subgroups in research and evaluation studies (etiological and genetic specificity), better identification of those specific components of intervention that are responsible for producing the desired effects, calibration of the intensity of the intervention and evaluation of better patterns of interaction between subgroups, based on the characteristics of children and families and of programme components (Guralnick 2005).

Our Symposium especially aims to promote an inter-disciplinary approach: ranging from theoretical and molecular genetics through neuroscience, environmental enrichment, the contributions of medicine and pharmacology and the different subfields of human development to the roles played by parents and carers.

Finally it also aims to present and discuss the possible convergence (which is no longer a question of science fiction) between genic therapies in humans and early neurobehavioural interventions.

## **ABSTRACT**

Title of conference: History of Early Intervention for Infants and Young Children with Down Syndrome: Where Have We Been and Where Are We Going?

Professor: Donna Spiker, Ph.D. Program Manager, Early Childhood Program  
Center for Education and Human Services  
SRI International, Menlo Park, CA, USA

Text: Fifty years ago, early intervention for infants and young children with Down syndrome did not exist in any comprehensive way. Beginning with a few experimental programs instigated by the advocacy of parents and the forward thinking of researchers, the field of early intervention for infants and young children with disabilities was born. In the past 50 years, there has been steady progress and significant changes in the practice of early intervention. Changes in our understanding of and research about the development of infants and young children with Down syndrome, the effects of early intervention on children and families, research on early development and learning more generally, and significant policy developments and changes in expectations about participation of persons with disabilities, including those with Down syndrome, in education and the community are all influencing what we know and how we think about early intervention.

In this presentation, an overview of the history of early intervention, with a particular emphasis on early intervention for infants and young children with Down syndrome, will be summarized. The history will include summaries about (1) the goals of early intervention for both the children and their families and how they have changed over the past 50 years; (2) research about the efficacy of EI as well as its actual implementation in practice; (3) how research in early childhood and early learning more generally has in the past and will in the future affect the practice of early intervention; and (4) how research and policy developments about older children and adults with disabilities, including those with Down syndrome, is influencing the practice of early intervention. Conclusions about where we have been with research and policy developments will be used to discuss implications for the future directions of the early intervention field.

## **ABSTRACT**

Title of the Conference: New perspectives of molecular and genic therapies in Down syndrome.

Professor: JM Delabar U.F.R. Biochimie  
Université Paris Diderot – Paris 7, Paris, FRANCE

Text: Aneuploidies, i.e. copy number disorders of functional genomic elements, are common genomic disorders with profound impact in the health of human populations. The phenotypic consequences of aneuploidies are numerous and range from mental retardation, developmental abnormalities, susceptibility to common phenotypes and to various neoplasms.

Trisomy 21 (Down syndrome, DS, T21) is the most frequent aneuploidy (1/700 births and 500000 patients in Europe) and it is still, even after the improvements of prenatal diagnosis, far outside the range of rare diseases (> 1/2000 in France). This is one of the main genetic causes of mental retardation.

New strategies which might allow countering some of the adverse effects of the phenotype have been assayed on mice models: these strategies are designed to operate during the development or at the adult stage. They are based upon recent discoveries on chromosome 21 genes properties and functions. Their effectiveness is evaluated by assessing characteristic phenotypes in different murine models with partial trisomies.

## ABSTRACT

Title of the Conference: Brain plasticity and environmental enrichment in Ts65Dn mice, an animal model for Down syndrome (DS).

Professor: Elizabeth Kida, MD, PhD New York State Institute for Basic Research in Developmental Disabilities New York, USA and Adam A. Golabek, PhD. New York State Institute for Basic Research in development Disabilities. New York, USA

Text: Brain plasticity is determined by both genetic and environmental factors. Brain abnormalities in DS subjects with hypocellularity, delayed myelination, dendritic and synaptic alterations, and abnormal neurogenesis have been relatively well characterized. However, the molecular bases of subnormal intellectual functioning of DS subjects have not yet been elucidated. It is also unknown whether, which, and to what extent abnormalities caused by triplicated chromosome 21 can be improved by environmental factors. Prior experiments in laboratory animals documented that an enriched environment (a combination of exercise, social interactions, and learning) alleviates behavioral abnormalities; improves spatial memory; increases neurotrophic support, the neural stem/progenitor cell pool, and neurogenesis; reduces synaptic alterations; and activates glutamatergic signaling. Encouraging data also were obtained in some animal models for human disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and fragile X syndrome. Thus, to address the issue whether environmental enrichment might have significant implications for the prevention and/or treatment of mental retardation in individuals with DS, we are using the most popular and best characterized animal model for DS, Ts65Dn mice. Our studies focus on the effect of enriched environment on the molecular aspects of synaptic plasticity and analysis of proteins associated with chemical synaptic transmission (synaptic vesicle trafficking, vesicle fusion, exocytosis, endocytosis, clustering of vesicles), some features of neurogenesis in the adult brain (cell divisions and proliferation in the dentate gyrus), and a potential to normalize or reduce increased levels of proteins encoded by triplicated gene, which are potentially associated with cognitive dysfunction in DS subjects (DYRK1A). Our data suggest that environmental enrichment can substantially alleviate some of the molecular abnormalities found in Ts65Dn mice, suggesting that it might also have therapeutic potential in humans with DS.

## ABSTRACT

Title of the Conference: Developmental Theory as a Context for Understanding and Evaluating Early Development and Intervention among Children with Down Syndrome

Professor: Jacob A. Burack, Heidi Flores, Cory Shulman  
McGill University, McGill University, Hebrew University of Jerusalem  
Hôpital Rivière-des-Prairies

Text: The current study of Down syndrome is essentially informed by the developmental approach to the study of the broader population of persons with intellectual disabilities. In his formalization and articulation of a developmental approach, Zigler (1967, 1969) revolutionized the scientific study of persons with intellectual disabilities by characterizing them within the lens of typical development, rather than within frameworks of differences, defects, and deficits. With this initiative, the developmental theories of Jean Piaget and Heinz Werner provided a context for understanding cognitive trajectories, sequences, and structures, and the focus of study was broadened considerably to include the "whole person", including issues of family environment, social relationships, and the personality-motivational factors that affect performance in both every-day life and laboratory settings. This transformation led to considerably more precise science with an emphasis on developmental level and the unique developmental pathways associated with the various etiologies of intellectual disabilities. As Zigler's initiatives were expanded by him and his colleagues, they included more fine-tuned discussions of etiology-specific profiles, such as those of persons with Down syndrome, within universal developmental frameworks (e.g., Burack, 1990; Burack, Hodapp, & Zigler, 1988; 1990; Cicchetti & Pogge-Hesse, 1982). Although this increasingly precise differentiation seem paradoxical with the implementation of a universal framework, the developmental approach continues to impact upon every aspect of theory, methodology, and interpretation in the study of children with Down syndrome and other etiologies associated with intellectual disabilities (Burack, Evans, Klaiman, & Iarocci, 2001; Flanagan, Russo, Flores, & Burack, 2008; Hodapp & Burack, 1989). The developmental approach provides a conceptual and methodological framework for expectations of the rates, trajectories, sequences, and profiles of development and for assessing and interpreting the impact of treatment on children with Down syndrome.

## ABSTRACT

Title of the Conference: Development of the Brain and Metabolism

Professor: David Patterson, Ph.D. Director of the Eleanor Roosevelt Institute  
Professor, Department of Biological Sciences  
University of Denver, Denver CO, USA

Text: Adequate nutrition of the mother and fetus before conception and during fetal development and development after birth has profound influences on brain and nervous system development. Supplementation with some compounds, notably folic acid, during these periods has been shown to reduce the incidence of certain neural tube defects. Some evidence has been presented suggesting that mutations in genes encoding enzymes and proteins that participate in folic acid uptake and metabolism can influence the prevalence of births of children with Down syndrome, or Trisomy 21. This observation remains unsettled, probably because of the complexity of the genetic and metabolic pathways involved and the complexity of the interaction between the genome and the environment. Other compounds such as choline and betaine have been shown to influence brain development during fetal development, sometimes with long term consequences for brain structure and function, in mouse models. A number of genes encoded on chromosome 21 are involved in metabolic processes, including those involved in folate, one-carbon, inositol, reactive oxygen species, and cholesterol metabolism. In some cases, mutations in these genes influence brain development and function in mouse models. In part because of this information, numerous attempts have been undertaken to ameliorate the intellectual disabilities seen in Down syndrome and other developmental and genetic disorders by nutritional means. So far, it is difficult to conclude that any of these have been objectively helpful. One difficulty is that comprehensive determinations of how Down syndrome affects metabolism have not been undertaken, although studies of individual metabolic pathways have provided some information. New methods of high throughput analysis of metabolism, applicable both to studies of humans and mice, allow new approaches to assess the possible metabolic consequences of Down syndrome. These analyses may be more immediately relevant to the phenotypes of interest than studies of alterations in gene or protein expression and may lead to new approaches to attempts to ameliorate the alterations in brain function and the intellectual disabilities that are features of Down syndrome. The rationale for these approaches will be discussed as will examples of the effects of nutrition on brain development and function.

## ABSTRACT

Title of the Conference: Early Medical Caretaking and Follow-up

Professor: Alberto Rasore Quartino. Coordinatore Comitato Científico EDSA  
Genova, ITALY

### Text:

Down Syndrome(DS)is associated with congenital malformations, immune deficiencies, leukaemia, cognitive impairment. In recent years therapies have been sought for, in order to improve the clinical conditions and reduce the cognitive impairment of the affected people. Long years of experience have demonstrated that early medical intervention is actually more effective both in the cure and in the prevention of secondary disabilities. Moreover, it is essential for the success of rehabilitation and social integration, resulting in a better quality of life of people with DS.

The surgical approach to congenital heart disease and gastrointestinal malformations will be discussed, as well as pharmacological treatments for thyroid disorders, leukaemia, short stature and other conditions of medical interest. Early intervention for correction of sensory defects will be examined. Early diagnosis for celiac disease and subsequent dietary changes can avoid serious consequences. Suggestions for appropriate diet and vitamin and mineral supplementations will be given. The importance of following health care guidelines will be stressed. A brief discussion on unconventional therapies will be made. They have been advocated with the object of remedying the intellectual impairment or phenotypic features, but unfortunately without any positive results, but only with negative effects on patients and often severe disappointments for the parents. Lastly a summary of new research on molecular biology of chromosome 21 will be exposed. Some genes localized on chromosome 21 are candidate genes for their disrupting effects on Ds phenotype and scientists are studying the possibility of reversing their negative action to correct the metabolic anomaly or the morphologic anomalies they cause.

## ABSTRACT

Title of the Conference: Cardiological assessment and surgery in Down syndrome

Professor: G.Dembour, department of pediatric cardiology, Cliniques universitaires St Luc, Bruxelles, Belgium

### Text:

Objective : Down syndrome (DS) is frequently (40-50% of DS patients) associated with congenital heart defects . Till the early nineties , cardiac surgery in these patients was considered as a high risk procedure.

At that time , some cardiologic centers questioned the advisability of repairing complete atrioventricular septal defects (CAVSD), the most frequent cardiac lesion in DS , because of the high postoperative mortality rate.

Currently, DS is no more considered as a risk factor for surgical repair, in comparison with eusomic population.

The aim of this retrospective study was to evaluate the risks and benefits of cardiac surgery in DS patients , in light of recent progress in surgical techniques and postoperative intensive care.

Methods: Between January 1992 and May 2008 , 106 DS patients (58 females and 48 males) underwent cardiac surgery.

50 (47.1%) presented with CAVSD ; 31 (29.2%) with perimembranous ventricular septal defect (VSD);

10 (9.4%) with ostium primum atrial septal defect (ostium primum ASD) ; 6 (5.6%) with isolated tetralogy of Fallot ; 4 (3.7%) with ostium secundum atrial septal defect (ostium secundum ASD) ; 2 (1.9%) with persistent ductus arteriosus ; 1 (0.95%) with sinus venosus ASD.

A total of 99 patients (93.3%) underwent primary repair ;7 patients with CAVSD underwent palliative surgery on a average of 12.4 months before repair.

Results : Early postoperative mortality (thirty-day mortality) was 5.6% (6 patients) ; 2 late deaths occurred due to extracardiac causes. 5 patients died early after CAVSD repair in the period from 1992 to 2000; none in the period from 2001 to 2008; 1 patient died early after VSD repair in 2002.

Postoperative morbidity included 2 patients with complete atrioventricular block requiring permanent pacemaker and 2 patients with hemiplegia (1 transient).

Reoperation was necessary in 4 patients after repair of CAVSD ; 3 patients for mitral valve incompetence, 1 patient for subaortic stenosis. Global incidence of reoperation was thus 4% ; 8.8% for CAVSD patients .

Long term follow up shows moderate mitral valve incompetence in 12 patients after repair of CAVSD; severe mitral valve incompetence is present in 5 patients who might require reoperation in the future.

Conclusion : Congenital heart defects in DS patients can be repaired with a low risk of mortality and morbidity. Constant progress in surgical techniques and postoperative care reduce progressively early and late complications after cardiac repair. Improvement of the described results could still be expected in the future.

## ABSTRACT

Title of the Conference: Enrichment and other environmental variables in an animal model of Down Syndrome. pharmacological contributions.

Prof. Jesús Flórez, M.D., Ph.D. Chair Professor of Pharmacology  
Facultad de Medicina, Universidad de Cantabria  
Santander, SPAIN

Text: Post-weaning enrichment of the environment (EE) is known to influence the expression of genes involved in neuronal structure, synaptic signaling and plasticity of the central nervous system (CNS) in normal animals. These morphological and physiological effects lead to increased spontaneous and exploratory activity, enhanced perceptive abilities, better performance and more efficient learning (see Wisniewski, this symposium). The question is whether genetic or chromosomal anomalies severely affecting mechanisms underlying cerebral development, such as occurring in Down syndrome (DS), would compromise the ability to respond to environmental stimulation in terms of neural plasticity and behavior.

A series of studies were performed in our laboratory on an animal model of DS, the partially trisomic Ts65Dn mouse, a widely used model for human trisomy 21. The studies were aimed at exploring the influence of post-weaning EE in Ts65Dn mice compared to their control littermates, under several environmental conditions. The main results were as follows:

1. Exploratory behavior was increased in trisomic mice.
2. Significant improvement of the spatial memory (Morris water maze) was observed in female trisomic mice, but was deteriorated in trisomic male mice.
3. Improved learning activity in female trisomic mice was not accompanied by increased dendritic spines, as opposed to control animals.
4. In the trisomic male animals, the excess of social and/or physical stimulation affected cognition by disturbing the emotional and behavioral components of the learning process.
5. Young male trisomic mice showed significant cell proliferation in the dentate gyrus of hippocampus.
6. The learning process of the Ts65Dn mice was improved pharmacologically by reducing the activity of the GABAergic system, an inhibitory system of the CNS which is known to be enhanced in DS.

We conclude that the CNS of the Ts65Dn mice shows neuroplastic responses to enrichment. However, significant differences are found when compared to control mice. The implications of these observations in the human context will be discussed.

## ABSTRACT

Title of the Conference: Aspects of Motor Development in Down Syndrome

Professor: Naznin Virji-Babul, Anne Jobling, Digby Elliott & Daniel J. Weeks

**Text:** This presentation will outline a conceptual framework for understanding motor development in persons with Down syndrome. Both physical and cognitive factors that influence motor development trajectories will be considered. Finally, we will discuss age related aspects of motor development that can provide opportunities for intervention that may enhance the acquisition of motor skills. An important point is that the considerable variability in motor development in persons with Down syndrome suggests that traditional methods of assessment and program development may not be useful in understanding task oriented behaviour.

## ABSTRACT

Title of the Conference: MEMORY DEVELOPMENT AND LEARNING

Professor: Stefano Vicari, Roma Responsabile di la Unitá Operativa di Neuropsichiatria Infantile, Ospedale Bambino Gesù Rome, ITALY

Text: Neuropsychological research has permitted defining different cognitive profiles among subjects with intellectual disabilities (ID) of different etiology. For example, numerous authors have stressed that the typical language profile for persons with Down syndrome (DS) consists of poor production with greater impairment of morphosyntax than of lexical abilities, but relatively preserved comprehension. On the contrary, children with Williams syndrome (WS) often show marked impairment in certain visual-spatial abilities (especially praxic-constructive) and relative preservation of both productive and receptive language, at least concerning the phonological elements. These observations seem to support a theoretical approach that considers ID not as a mere slowing of normal cognitive development, but as distinct, individual profiles, that can be qualitatively specified. The importance of this approach was evidenced in several recent studies of memory, especially implicit memory in subjects with ID.

The neuropsychological studies reported in literature suggest insufficient development of the mnesic function in ID at different levels of articulation. Long-term memory (LTM) has been extensively investigated in persons with ID both in the explicit and in the implicit component. According to recent studies, persons with ID should show a diffuse impairment of declarative mnesic abilities and a relative preservation of implicit memory.

Our current focus is on the characteristics of LTM and STM memory in children with ID and, particularly, with DS. Our results are relevant for our knowledge on the qualitative aspects of the anomalous cognitive development in mentally retarded people and the neurobiological substrate underlying this development. Moreover, our findings suggest specific intervention procedures to improve quality of life of people with DS.

## **ABSTRACT**

Title of the Conference: Speech perception, stimulation and phonological development

Doctor: Michèle Pettinato

Text: Research on typically developing children has shown that within the first year, infants learn to recognise the sounds of their native language and segment words from fluent speech. Although Down syndrome is known to be associated with a high incidence of audiological problems, little is known about early speech perception abilities in infants with Down syndrome and how these relate to later language development. Indeed, the majority of the literature on phonological development in Down syndrome has concentrated on the production of phonology, and it has been suggested that difficulties originate mainly in the assembly and rhythmic ordering of speech sounds. However, a comparison of the literature on children with cochlear implants, who also receive degraded auditory input in their early development, reveals some striking similarities in the phonological development of the two populations. These will be explored during the talk as well as work relating to speech perception in Down syndrome. It will be argued that in order to be able to design effective early intervention methods, speech perception in this population needs to be more comprehensively investigated. Methodological difficulties will be described and new tasks which may avoid these will be presented.

## **ABSTRACT**

Title of the Conference: Early prosodic sensitivity, communication, language development, and training

Professor: JEAN-ADOLPHE RONDAL, Ph.D., Dr. Sc. Lang.  
Emeritus Professor of Psycholinguistics, University of Liège  
Professor of Language Psychology, Università Salesiana, Venice

Text: As research suggests typical language development starts three months before birth with the exposure of the fetus to maternal voice. At birth, the typically developing baby already recognizes her/his mother's voice and tongue relying on acoustic and prosodic characteristics. We still know nothing regarding this basic episode in babies with Down syndrome and/or related congenital genetic conditions. The presentation will draw attention on this question given that there are reasons to suspect that these babies do not dispose of the same language experience as early in life as the typically developing ones which probably impinges on their language development and contributes to early delays. Communication between babies with Down syndrome and related conditions and their caretakers will be analyzed in the perspective of early lexical development. The transition towards syntactic development will also be dealt with. Training strategies able to boost development and reduce delays will be defined.

## **ABSTRACT**

Title of the Conference: Teaching reading in early years at home and preschool

Professor: Sue Buckley Director of Science and Research  
Down Syndrome Education International, Portsmouth, UK.

Text: In this presentation I will explain why it is important to engage children with Down syndrome in reading activities from an early age – and therefore for teachers in early intervention services to know how to do this. I will endeavour to review relevant research and identify the ways in which we can go from research to practice.

I will briefly explain what we know about the reading progress of children with Down syndrome and set this in the context of what we know about their specific learning profile and their speech and language development. This should show why reading may be a particularly effective way to help children learn to read and improve their spoken language and verbal memory skills.

I will explain the steps that will lead to successful reading and language learning and illustrate my presentation with new video clips from our own work with preschool children from 2 to 5 years of age. I will also show examples of the teaching programme 'See and Learn' which we are developing to help parents and practitioners to teach children to read and to use reading activities to develop spoken language.

This last point is important. Some children with Down syndrome find reading easy and learn to read words and sentences quickly, others learn much more slowly. However, all children can benefit from reading activities to develop their understanding and use of spoken language over time – even those who do not become independent readers.

Finally, I will stress that in these early years, it is usually parents who teach their children to read with the support of those in early intervention and speech and language services – and make a plea for those professionals to provide this support.

## ABSTRACT

Title of the Presentation: The role of parents in early intervention

Professor: Gerald Mahoney Director. Center on Intervention for Children and Families

Mandel School of Applied Social Sciences. Case Western Reserve University. Cleveland OH, USA

Text: In this presentation research related several issues regarding the role that parents play in early intervention for children with Down syndrome and other disabilities will be reviewed. This will include the following research findings: (1) that how parents interact with young children with Down syndrome accounts for a major portion of the variability of the cognitive and communication outcomes these children attain during the first three years of their lives; (2) that how parents interact with children with developmental disabilities during the early childhood years is related to children's academic and developmental attainments in later childhood; (3) that the developmental outcomes children attain in early intervention programs that do not work with parents are related to parents' style of interacting with their children, but not to the type of intervention children receive; and (4) that the effectiveness of early intervention is highly associated with the impact that intervention has on parents' level of responsiveness with their children.

In addition, research related to the way that early intervention programs have worked with parents will also be described. Methods of parent involvement that will be discussed include: family support services; parent groups; behavioural training; parental observations of intervention sessions; and coaching parents on the use of responsive interaction strategies with their children. Research will be described which indicates that the only form of parental involvement that has been consistently demonstrated to enhance children's development and/or social emotional functioning in early intervention have been those that have encouraged parents through coaching to learn and use responsive interactions with their children. Research will be described that indicates that this approach to intervention has been effective at promoting children's cognitive, communication and social emotional functioning. Research will also be described which suggests that these effects are related both to the impact that this approach has on the quality of parent-child relationships as well as to the fact that responsive interaction strategies encourage children to practice and use their current developmental behaviours and concepts.