EUROPEAN SCIENCE FOUNDATION CONFERENCE

"Gene–environment interaction in early human development: demonstration project on orofacial clefts"

3rd International Collaborative Workshop

Dates: Friday 19th / Saturday 20th May 2000

Arrival &Transport:

Thursday 18th May 2000 Arrival in Edinburgh or Dundee. Transport laid on for carriage to hotel accommodation. It is important that when you book your flights you send the arrival and departure times at Edinburgh Airport to Rosemary (r.c.inglis@dundee.ac.uk) so that transport can be arranged.

Delegates Hotel:

Woodlands Hotel, 13 Panmure Terrace, Barnhill, Dundee. DD5 2QL (see Brochure)

Location: 10 mins from City Centre. Setting: Beautifully appointed and landscaped with superb facilities including Health Club. Excellent reputation.

Conference Venue:

Discovery Conference Centre, Discovery Quay, Dundee DD1 4XA (see Brochure)
One of Scotland's foremost visitor attractions.

Outline Programme:

Thursday 18th May:

Executive Committee Meeting at 6.30 p.m. at Discovery Centre followed by evening meal.

Friday 19th May: Day 1 of Conference

08.20 Arrival / Registration / Coffee

Session 1 : Nutrition in the context of gene/environment interaction: Chairman: Peter Mossey

08.50 Introduction **Professor Nigel Pitts**

09.00 Nutritional epidemiology – diet and dietary supplements in orofacial clefting **Professor Julian Little**

09.20 Dose dependent effect of folic acid on the Prevention of OFC **Professor Andrew Czeizel**

09.40 Cleft lip, cleft palate and the folate metabolic pathway **Dr Edward Lammer**

10.00 Folate and beyond: under-studied nutrients and populations **Dr Ron Munger**

10.20 **DISCUSSION**

10.30 COFFEE

Session 2 : Update in gene/environment interaction studies underway in four European Centres

Interaction of Maternal Nutrition and Folate Metabolic Factors in Orofacial Clefting (ongoing European studies) : *Chairman: Professor Elisa Calzolari*

10.50 UPDATE ON COMMON CORE PROTOCOLS PROJECT **Dr Sylvaine Cordier**

11.00 **Denmark** Professor Kaare Christensen

11.15 **Norway** Professor Rolv Terje Lie

11.30 **Scotland, Manchester/ Liverpool** Dr Peter Mossey

11.45 **France** Dr Sylvaine Cordier

12.00 **Netherlands** (on behalf of Dr Regine Steegers)

12.15 –12.30 *Questions / Discussion*

12.30 –2.00 pm **LUNCH**

Session 3: Data analysis methodology: Gene identification & analysis:Chairman: Dr Reynir Arngrimsson

2.00 The quest for candidate genes in OFC **Natalie Prescott**

2.15 Candidate gene identification – an update **Dr David FitzPatrick**

2.30 Analysis of case / parent triad data - exploration of study methodology
Dr Alan Wilcox

2.50 Update on gene-environment interaction research & application to OFC
Dr Lorenzo Botto

3.10 **Discussion**

3.30 **TEA**

Session 4 : Data analysis methodology II and pathogenesis of OFC: DrPeadar Kirke

3.40 Use of familial archives in orofacial clefting research **Dr Alfred Arnason**

4.00 The analysis of maternal nutrition using Biochemical markers
Dr Joe Mc Partlin

4.20 Is intrauterine growth retardation a pathogenetic mechanism in OFC
Professor Andrew Czeizel

4.50 **DISCUSSION**

7pm for 7.30 Conference Banquet at the "Lands of Loyal" Hotel, Alyth
Address: Alyth, Perthshire, PH11 8JQ Tel: 01828 633151
URL: http://freenet.co.uk/homepage/lol-hotel

Saturday 20th May (Day 2 of Conference)

Session 5: Pre-Workshop presentation:

9.00 – 9.30: Pathogenetic classification of Orofacial Clefts – **Professor Christi Vermeij-Keers**

9.30 - 10.30: *Session 6 : Workshops* :
Analysis of gene/environment interaction with data collected in European studies

Workshop 1: Combined analysis in gene-environment interaction studies (gene – gene, environment – environment and gene-environment interactions)
LEADERS: **Professor Rolv Terje Lie / Dr Alan Wilcox**

Workshop 2: Prioritising environmental factors and genes for further gene/environment interaction hypotheses in orofacial clefting - smoking, alcohol and nutritional factors
LEADERS: **Dr Sylvane Cordier / Dr Lorenzo Botto**

Workshop 3: The role of genetics in orofacial clefting: – association and linkage analyses ?
LEADERS: **Professor Sue Malcolm / Dr David FitzPatrick**

10.30 – 10.50 Coffee

10.50 –12.00 ***Plenary Feedback, Discussion & Future Planning***

Three feedback sessions of **10 minutes** duration plus half an hour for Discussion

12.30 pm Tour of the Discovery, and other optional sightseeing tours can be arranged

Please note:
We acknowledge that an overnight stay on Saturday night is likely to make a significant difference in the cost of a return flight and for this reason those who wish to stay at the Woodlands Hotel on Saturday night will NOT be charged extra for the Saturday night accomodation and breakfast.

The Banquet on Friday night is at a prestigious venue 15 miles out of Dundee and to cover the cost there will be a supplementary charge of approximately £20 per head.

EUROPEAN SCIENCE FOUNDATION CONFERENCE

SCIENTIFIC REPORT

"Gene–environment interaction in early human development: demonstration project on orofacial clefts"

3rd International Collaborative Workshop

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Conference Venue:

Discovery Conference Centre, Discovery Quay, Dundee DD1 4XA

SCIENTIFIC REPORT

European Science Foundation Network Meeting 18th/20th May 2000

Session 1 : Nutrition in the context of gene/environment interaction: Chairman: Peter Mossey

Professor Nigel Pitts, Dean of Dentistry at the University of Dundee launched the Conference and mentioned the significance of the venue, Discovery Point, with Captain Scott's ship, the Discovery being a symbol of research. He also outlined the importance of multi-disciplinary research and in the field of craniofacial anomalies the importance of collaboration.

Professor Julian Little (Aberdeen, Scotland) gave an overview of Nutritional Epidemiology and the state of nutritional research in birth defects and the field of orofacial clefting in particular. Professor Little concluded that the evidence is inconsistent, perhaps due to methodological differences but also because of failure in the past to investigate gene/environment interaction. He went on to elaborate on biochemical markers of nutrition and in particular the folate/homocysteine pathway. Professor Little also looked to the future where analysis of dietary supplements as well as food intake would be important. He outlined some of the interpretation problems such as the relationship with total energy intake and examining specific nutrients in the diet and the problem of specifying hypothesis when examining gene/nutrient interaction.

Professor Andrew Czeizel (Hungary) presented the Hungarian data on diet and multi-vitamin supplements in peric-onceptional care. This data provides evidence that multi-vitamin supplements including a physiological dose of folic acid reduces the first occurrence of neural tube defects but does not appear to be protective against the occurrence of oral clefts. Professor Czeizel then turned his attention to those studies where a higher dose of folic acid supplement was provided in the peri-conceptional and/or first trimester of pregnancy. These data reveal that a high dose of folic acid (6 mg) during the critical period for orofacial clefts, there is some evidence of a preventive effect – but only for non-syndromic orofacial clefting. This supports the notion of a possible dose response effect with regard to the prevention of cleft lip and palate. He also concluded that this issue was worthy of further research which would be necessary before proceeding to Public Health recommendations to increase the dose of folic acid in the peri-conceptional period.

Dr Edward Lammer (California, USA) explained the biochemical effects of the MTHFR polymorphism which is significant in folate metabolism in that the enzyme due to the genetic polymorphism has 50% reduced activity and results in an elevation of plasma homocysteine. Further investigation of the effect of the reduced enzyme activity, there is no evidence of an increased risk for those children with the genotype that confers the lower enzyme activity. Dr Lammer did, however, note the inconsistency between a study carried out in California and a similar MTHFR study in Ireland. In the Irish study a statistically significant increase in risk was noted in association with homozygosity for the TT allele in an orofacial clefting group compared to controls. He concluded that further research is required to examine the significance of the MTHFR in both cleft palate and cleft lip and palate and this should be examined in the context of gene/environment interaction.

Session 2 : Update in gene/environment interaction studies underway in four European Centres

Dr Sylvaine Cordier (France) presented the aims and objectives of the common core protocols project which was one of the first goals outlined by the ESF Network in Paris in July 1998. It was agreed that the objective should be to publish these as an ESF publication, prior to which a document would be drafted and circulated to all those interested in future research in the epidemiology and aetiology of orofacial clefts. Dr Cordier outlined the topics that would constitute the common core protocols and those who had agreed to take a lead on the various components.

Dr Kaare Christensen (Denmark) outlined the aims and objectives of three major studies in Denmark, the largest of which is a prospective study of 100,000 women who are interviewed early in pregnancy. This cohort study is concerned with all congenital malformations. The design of this study has been informed by the previous studies. In the first of these in the early 1990's an association with smoking as a risk factor was detected. In a second study on gene/environment interaction, the TGFa polymorphism which is very common in Denmark was not found to be a risk factor for clefting either. This prospective study that is currently underway will provide a wealth of information on diet, lifestyle factors, maternal medical history and genetic susceptibility for various birth defects including clefts in the future.

Professor Rolv Terje Lie (Bergen, Norway) outlined the progress with the Norwegian prospective case control study which is similar to the project being carried out in Denmark – at least in its overall aims. This began in 1996 as a retrospective case control study and is progressing to a prospective cohort study. From the cases information on environmental exposures, nutrition and medical history are collected. In terms of DNA, blood samples collected from the child and the aim is to collect both buccal swabs and blood from both parents. These data will enable case triad and case control studies and gene/environment interaction in the Norwegian population.

Dr Peter Mossey (Dundee, UK) outlined the data that are being collected in respect of the Wellcome funded UK based case control study. This is very similar to the studies being carried out in Denmark and Norway, on additional questionnaire which is part of the UK study is that which collects information on stress/distress in the early stages of pregnancy. Also, there is a particular emphasis on the folate hypothesis and in the maternal medication section the questionnaire is tailored towards the folate hypothesis – in that we are looking specifically for drugs that may effect metabolism of folate and folate antagonists. Another difference from the Scandinavian studies is the collection of a maternal blood sample one year after the birth of the child. From this case control comparisons of red cell folate, plasma folate, Vitamin B6, B12, homocysteine and methylmalonic acid are carried out. Dr Mossey also outlined some of the practical problems with the study and outlined briefly the types of analyses which are planned.

Dr Sylvaine Cordier (France) presented the practicalities of a similar case control study being undertaken in France. There were also a few differences in the French study in that it started out as a hospital based case control study because of difficulties setting up population based studies.

The DNA is being obtained from blood samples taken from child and both parents. This was also the protocol for controls but difficulties were experienced in recruitment of controls on the basis of obtaining blood samples. An alternative to a case control design would be to use the case triad approach to find genes and investigate gene/environment interaction in the cases only. This raised the question as to whether results of gene identification from case triads has been compared to that in the case controls, this would validate the traid approach of similar results doing these different types of analyses were noted.

Dr Regine Steegers (Netherlands) is another collaborator in the ESF International collaborative case control study and again there are many similarities with the data being collected elsewhere. The differences in the study methodology include collection of blood samples for the purposes of biochemical analysis and DNA, as well as buccal swabs for DNA in those for whom blood is not obtained. Also urine samples are collected from the mothers. The matching criteria for controls include the identification of mothers who attended the same ante-natal clinics as the mothers of the index children. The design includes a 50-50 split in the recruitment in terms of home based and hospital based recruitment, the only difference being that blood samples are taken in the hospital study and buccal swabs or mouthwashes in the home based study. The biochemical and DNA analysis are ongoing in parallel with the data collection and it is hoped that the gene/environment interaction data analysis can begin before the end of the Year 2000.

Session 3: Data analysis methodology: Gene identification & analysis:Chairman: Dr Reynir Arngrimsson

Dr Natalie Prescott (London, UK) described the research at the Institute of Child Health in London aimed towards investigation of the genetic aetiology of non-syndromic cleft lip with or without cleft palate. The objective of this research was a whole genome scan of effected sib-pairs to try identifying regions of the genome which is shared more often than would be expected by chance. Having identified gene locations, the objective is then to find positional candidate genes in these loci and use TDT analysis to find linkage. 92 sib-pairs were used for the whole genome scan with a resolution of approximately 4½ centimorgans with an information content of almost 80%. One significant finding with regard to the folate hypothesis is that TDT revealed an association with the MTHFR 1298 polymorphism. The over-transmission to affected individuals was statistically significant and is worthy of further investigation.

Dr David FitzPatrick (Edinburgh, Scotland) highlighted the vast amount of genetic information available and contrasted the approached of human geneticists who are interested in developmental pathways and genetic epidemiologists who examine the metabolic pathways of exposure such as alcohol, smoking and folate. These are inter-related but we need to have a rational approach in deciding what pathways in genes should be examined and how. He went on to list his six criteria for ranking candidate genes -

1. Cytogenetic clues such as reciprocal translocations: Recurrent break points with associated abnormal field types and picking up those that have orofacial clefting and phenotype.
2. Expression patterns in developmental site- and stage- specific phenotype, an example is TGFα which in association studies is good but from expression pattern it is not.

3. Genetic linkage and association clues.
4. Phenotypic similarity to animal mutant models such as TGFβ3 in mice.
5. Phenotypic overlap with a human mendelian genetic disorder.
6. Biological function and linking with plausible genes such as those in the folate pathway.

A good way of encouraging collaboration and sharing information is by means of a Web based database and there are many candidate genes for cleft palate but very few for cleft lip due mainly to the fact that developmental phenomenon cleft lip is much less studied. By posting this database on the Web it could be a resource for all researchers involved to keep the database up to date. Another innovation is to use 3 dimensional models on the computers to build up and paint gene expression patterns on mouse embryos and working chronologically through the period of time that is critical for craniofacial development. This would enable visualisation of gene expression patterns during development.

With regard to the folate pathway and MTHFR, this appears to be an opportunistic candidate rather than an evidence based biological candidate. TGFβ3 is an excellent candidate biologically for cleft palate but not for cleft lip. MSX1 is a good candidate for cleft lip and a family study was recently published with and MSX1 mutation associated with cleft lip and palate and hypodontia.

Session 4 : Data analysis methodology II and pathogenesis of OFC: DrPeadar Kirke

Dr Alfreo Arnason (Iceland) presented pedigree data from Iceland and showed numerous examples to provide evidence of familial transmission of cleft palate and cleft lip and palate. Dr Arnason also gave a comprehensive overview and history of the story behind X linked cleft palate and ankyloglossia which was diagnosed in the Icelandic population. One unusual feature in the Icelandic families is the fact that some pedigrees show cleft lip and cleft palate in the same pedigrees. The high level of ascertainment and pedigree detail as well as the historic nature of this Icelandic data makes this an extremely valuable resource for orofacial clefting research.

Dr Joe McPartlin (Dublin) presentated the next paper on behalf of Professor John Scott. Dr Joe McPartlin from the Department of Biochemistry, Trinity College, Dublin presented comprehensive and practical details on methodologies and protocols for blood collection related to research relevant to the audience. Dr McPartlin is involved in the analysis of various nutrients for the UK and Netherlands case control studies. Helpful, practical tips were provided on the methods of blood collection, the processing and storage of samples, the biochemical procedures involved in obtaining red cells from an EDTA sample and the procedures involved in obtaining plasma for the estimation of Vitamin B6, B12 and homocysteine. It is also possible to extract lymphocytes and these lymphocyte pellets can be suspended in foetal calf serum and stored in -80°C freezers. He emphasised the importance of accurate transcription during the labelling of tubes and provided tips on the shipping of samples which an inevitable part of international collaborative studies.

Dr Lorenzo Botto (CDC, USA) began by describing the hopes for participating in a multi-centre study in the USA. This is a case control study in which eight centres will collaborate and

hopefully 1,600 interviews will be carried out over a five year period. One of the objectives of this study is to provide information on gene/environment interaction. The important aspects of future research however will be which genes and which environmental factors and this is the value of these international collaborative efforts. Dr Botto projected how the data that is available will be analysed in the future in this field in the expectation that we will have multiple genetic markers. It will be important to define the prevalence of genetic polymorphisms in the population and define sub-populations on this basis so that these can be taken into account in the analysis. It would also be nice if there were a common core protocol in the way that data is analysed and displayed – another idea for common protocols in large international collaborative studies. Every method has its own merits and e.g. case only and case triad approaches are valuable but may not be the answer to everything and we may need to swing back to a case control approach to provide information on different hypotheses.

Dr Alan Wilcox (NIEH, USA) outlined the advantages and limitations of the analysis of case parent triad data. It is especially good for diseases that are apparent at birth or at childhood so that access to parents is possible. Secondly, the cases do not have to representative of the population and, of course, no controls are required. The most common method of analysis for multi-factorial disorders is the transmission disequilibrium test (TDT); and in this analysis there is no consideration of how the genotype of the mother may be contributing. In contrast along the log linear model enables independent estimates with the same data set of the risk associated with the allele if it is carried by the mother or if it is carried by the offspring. This is also useful in the understanding of parental imprinting for the detection of alleles imprinted by the father or the mother. The log linear model is also able to obtain some useful information even if one element of the triad is missing. Dr Wilcox went on to describe how it is possible in a case only study to detect the effect of an environmental factor when there are no controls. This is done by stratification of all triads by the exposure of interest – and then test for the strength of the genetic association of each of these strata. The problem is, however, that there is no frame of reference so controls would be required to determine whether an exposure is being protective in one allele or harmful in the other allele. It is also important to appreciate that without controls it is not possible to disprove the dependence between the gene and the exposure as the case triad approach in looking at gene/environment interaction must assume that the gene and the exposure are not associated. In summary, while case parent designs and case control designs have their own merits the preferred study in gene/environment interaction research is to be able to do a hybrid of both.

Professor Fabrizio Bianchi (Italy) illustrated the preliminary results of an analysis of the EUROCAT Registry data which contributes significantly to knowledge concerning epidemiology and time trends for orofacial clefts in Europe over the last two decades. The database included 8,700 cases from multiple centres with an overall rate of 0.6 per 1,000 for cleft palate, 0.35 per 1,000 for cleft lip and 0.57 per 1,000 for cleft lip and palate giving a total of 1.51 per 1,000 throughout Europe. These stillbirths constituted 3.8% of the total and the sex ratio overall was 0.8 for cleft palate, 1.6 for cleft lip and 1.75 for cleft lip and palate. Associated anomalies were present in 20% of cleft palate, 11% of cleft lip and 17% of cleft lip and palate patients.

Dr Bianchi went on to point out the regional and geographic variations. His general conclusions were that there is significant heterogeneity in Europe and even between different regional centres

in one country. The groupings as described are still too large and heterogenous and a recommendation must be to more carefully define sub groups to determine whether there are more homogenous sub groups. Consensus would be required on how this is best done but it is useful to have collaborative groups such as this one to discuss these issues and ultimately extra resources will be required to facilitate this.

Session 5: Pre-Workshop presentation:

The final speaker was **Professor Christi Vermeij-Keers** from the Department of Plastic and Reconstructive Surgery at the University Hospital in Rotterdam who addressed the controversy that exists on the classification in orofacial clefts. This included a detailed and superbly illustrated instructional session on early craniofacial development – illustrating the mechanism for fusion between the embryonic facial processes, failure of which results in cleft lip and at a slightly later stage cleft palate. Professor Vermeij-Keers presented a rationale for the sub-classification of cleft lip and palate based on whether these are fusion defects or differentiation defects, for instance, in the case of a complete cleft in the lip this will always be a fusion defect while an incomplete cleft in the lip where there is a tissue bridge will be a differentiation defect with a different chronological time frame and with a different aetiology. It is also possible to have both simultaneously such as a differentiation defect in the primary palate and a fusion defect of the secondary palate.

EUROPEAN SCIENCE FOUNDATION CONFERENCE
19th-20th MAY, 2000 – DUNDEE

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