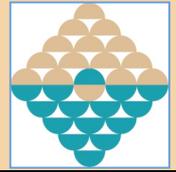


Boyne Research Institute

Annual Report 2010

Twenty Years on & New Directions

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Twenty Years on & New Directions

Mission The joint missions of the Boyne Research Institute comprise research and education. Our research mission is to help understand the causes and consequences of diseases during childhood. Our current projects include studies into the causes of birth defects in families, development of Irish young people and their adult achievements (the Drogheda School Leavers Cohort) and the long-term complications of cancer during childhood. Our educational mandate is to provide research experiences for young people from the community, and training for junior scientists.

Objective While retaining our present structure of independence and our community base, we are committed to becoming a world-class research institute. We aim to achieve this by expanding partnerships to complement our capabilities.

Goals for the Next Five Years Development of BRI's capacity to carry out joint epidemiologic-molecular projects with our research partners is a major part of our vision for the next five years. We also aim to expand our student training programmes to include more third-level and post-graduate students from Ireland and from overseas. Expanding our sources of research and training funds is a major prerequisite for these goals.

Website The website of the Boyne Research Institute carries more information on the research approach, publications, presentations and results of our studies. Please visit www.boyneresearch.ie. You can also obtain reprints and reports of our studies from admin@boyneresearch.ie.

From the Director

*New directions after nearly 20 years of research by the Boyne Research Institute in Drogheda. The new direction takes the form of an EU-funded grant to a consortium called **PanCareSurFup**, of which the Boyne Research Institute is a participant. New directions also includes moving the Institute to new premises in Drogheda. Our old premises in Duke House, Duke Street, had become too dilapidated for our purposes.*

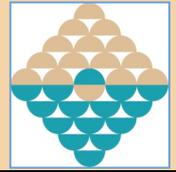
The new premises at Tiernan House, Fair Green, Drogheda, includes state-of-the-art audio-visual equipment. Moving took place in November, 2010.

Our membership in the PanCareSurFup consortium, brings the Boyne Research Institute into the company of some of the best minds in Europe focused on late effects after childhood and adolescent cancer. The consortium is funded by the Seventh Framework Programme of the EU (FP7). The website for PanCareSurFup should be live early in 2011, and will be called www.pancaresurfup.eu. Here you will see the list of members and the array of activities planned for our consortium for the next five years. From research that several of us have been involved in and continue to work at, we know that cancer and its treatment during childhood and adolescence carry significant complications for many survivors. We plan to investigate many aspects of these issues, to prepare guidelines for long-term care, and disseminate the research results and guidelines widely, to professionals and the lay community alike. The project arises from PanCare (www.pancare.eu) a new network of professionals and survivor/parent groups, dedicated to ensure that every European child or adolescent with cancer receives optimal long-term care.

Our work with Irish Families with Neural Tube Defects brings its epidemiologic aspects to a close with the publication of the final results from interviews with three generations in the participating families. New collaborations with molecular scientists are helping to develop our findings further at the subcellular level, and investigate new mechanisms of inheritance.

I am grateful to the staff, volunteers and board members for their support and good will throughout the year. Support from the local community and from friends and foundations in the United States continues to be crucial. Many blessings on you all.

Julianne Byrne, Director



SUMMARY OF RESEARCH RESULTS FOR 2010

1. **STUDIES INTO THE GENETIC ORIGINS OF NEURAL TUBE DEFECTS**

Project Title: Irish Families with Neural Tube Defects

Overall Objective: to uncover evidence of inheritance patterns within families where an individual has been born with a neural tube defect (NTD). Markers of inheritance patterns with underlying genetic susceptibility are birth defects and adverse pregnancy outcomes (miscarriages, stillbirths and preterm deliveries). Ultimately, a diagnostic test may use these factors to determine who is most at risk of having a child with a birth defect, or a pregnancy that ends adversely.

Methods: Between 1995 and 2002, 79 Irish families with NTDs participated in this research project of the Boyne Research Institute in Drogheda. The first phase consisted of an interview with the nuclear family (parents), covering the health of the proband and family members, including a reproductive history. In subsequent phases we interviewed uncles and aunts, first cousins, the proband and siblings. In 2007, BRI carried out a study of folate status among 325 relatives (of all types) in these families. Molecular genetic analysis of 5 single nucleotide polymorphisms was done in 2008 in collaboration with CDC in Atlanta.

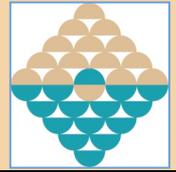
Results: Maternal relatives in these families have more birth defects overall, including more NTDs, than paternal relatives, and than expected based on the general public. This tendency is present in three consecutive generations (uncles/aunts, first cousins and first cousins once removed), without any suggestion of attenuation (*epub, 2010*).

In addition, pregnancies to first cousins were less likely to end in miscarriage if the mother took supplemental folic acid tablets before or during early pregnancy. That folic acid helps prevent birth defects, including neural tube defects, has been accepted for some time. Our study of first cousin pregnancies also showed a reduction of birth defects in women who took folic acid as recommended. But the extra benefit of folic acid in reducing miscarriage rates is not as widely known (*epub, 2010*).

Results from our serum folate study (2007) showed that low levels of serum folate were unlikely to explain the patterns of excess risk of birth defects among maternal relatives (*submitted for publication*). However, results from the molecular genetic analysis of 5 SNPs showed significant associations of some polymorphisms with maternal relatives (*results being prepared for publication*).

CONCLUSIONS

This pattern of preferential maternal inheritance has been reported in many previous studies for neural tube defects alone, and for the first time by the Boyne Research Institute for birth defects overall. In addition, our studies show persistence of this pattern through three generations of the same families. The pattern suggests that some factor is travelling along the maternal line that brings extra risk of birth defects. The factor may be genetic, that is, linked to genes and DNA, or it may be some other alteration in the cell. We are currently investigating these possibilities. The implications for public health are clear: family members, especially those related through the mother, really should be taking folic acid as recommended.



2. LATE EFFECTS AFTER CHILDHOOD CANCER

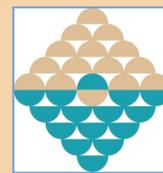
Overall Objective: The objective of this project is to initiate and carry out research studies into the long-term consequences of cancer during childhood to survivors and their families in a European context.

Background: Survival after childhood cancer approaches 80% in developed countries. The long-term consequences of cancer and its treatment include second cancers, deficits in fertility and cognitive functioning for some, but not all survivors. As treatments evolve and improve, continued follow-up of existing and new cohorts of survivors is needed to provide accurate and timely information for survivors to prevent and remediate where possible the long-term consequences of cancer and its treatment.

2010 Activities

1. **Survival after childhood cancer in Ireland:** BRI collaborated with staff from the National Cancer Registry of Ireland on an analysis of their data. The objectives were to update survival rates and to evaluate socio-economic disparity, that is, to see if children from disadvantaged families had lower survival rates.
2. **US Study of Childhood Cancer Survivors (CCSS):** Dr. Byrne was a co-author on a report on female fertility from this study (Daniel Green, principal author). See publication list below.
3. **PanCare:** The Boyne Research Institute is a founder member of a Pan European consortium to establish a Europe-wide study of childhood cancer survivors called **PanCare** (www.pancare.eu). PanCare meets twice yearly. Dr. Byrne is a member of the structural committee and the website committee.
4. **PanCareSurFup (PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies):** The Boyne Research Institute is a participant in this 16-member consortium from 11 European countries, approved for funding in April 2010 by the European Union's 7th Framework Programme (FP7). The objectives of this 5-year project are to:
 - a) Establish a retrospectively ascertained pan-European cohort of survivors of childhood cancer within which the occurrence of late mortality, second malignant sarcomas and carcinomas, and cardiac events can systematically ascertained and validated.
 - b) Undertake individual patient radiation dosimetry for individuals included within the nested case-control studies to obtain estimates of dose to the site of development of the adverse event and the corresponding site in the matched controls.
 - c) Estimate the absolute risk of these adverse health outcomes within the cohort and compare observed and expected numbers of events where general population rates are available to enable the calculation of expected numbers. Of particular interest will be the comparison of observed and expected numbers among those aged over 40 years.
 - d) Execute three nested case-control studies of cardiac disease, second malignant sarcoma and second malignant carcinoma, respectively, and one cohort study of late mortality, to determine the aspects of radiotherapy and type and dose of chemotherapy associated with increased risk.
 - e) Produce clinical follow-up guidelines for health care professionals, survivors and their families based on existing evidence and the results from this study in terms of the absolute risk available from the cohort studies and the relative risks in relation to risk factors from the case-control studies. This includes issues related to transition from a paediatric to adult environment for on-going follow-up.
 - f) Establish partnerships between providers and survivor/parent groups to disseminate information about PanCareSurFup to the general public, to health professionals and survivor/parent groups; train health care professionals through conferences, workshops, booklets and web based information; empower and educate survivors to be as informed as possible to optimise their future well-being.

The Boyne Research Institute is represented in all 8 work packages of PanCareSurFup; Dr. Byrne is also the deputy coordinator of the study, and the deputy manager of WP7, which is the dissemination and training work package. For more information, please visit the website, www.pancaresurfup.eu.



MEETINGS & PRESENTATIONS

1. PanCare Meetings in 2010: Spring meeting in Paris at Institut Gustav Roussy, and Autumn meeting in Mainz at the invitation of the German Childhood Cancer Registry.

COLLABORATIONS

- ❖ Dr Paul Walsh, Dr. Harry Comber, National Cancer Registry of Ireland, Cork, Ireland
- ❖ Dr RJ Berry, National Center on Birth Defects & Developmental Disabilities, Centers for Disease Control & Prevention, Atlanta, GA, USA,
- ❖ Dr. Lars Hjorth, University of Lund, Sweden (chairman, PanCare & coordinator, PanCareSurFup)
- ❖ Dr. Daniel Green, Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, Memphis, TN, USA
- ❖ Dr. James Korelitz, Westat, Rockville, MD, USA.

OVERSIGHT OF THE BOYNE RESEARCH INSTITUTE, 2010

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We are grateful to those members of our Board of Trustees and the Ethics Board who give freely of their time and energy to help advance the mission of the Boyne Research Institute. The Board of Trustees meets quarterly. The Ethics Board reviews each new project while in the planning stage. We especially appreciate the *pro bono* services of Apt Media (<http://www.apmediainc.com/index.php>), its principal Kim Bieler, staff Mark Eberman and colleagues for website development and graphics.

PUBLICATIONS, 2010

- Byrne J. Three generations of matrilineal excess of birth defects in Irish families with neural tube defects. Accepted for publication, Irish Journal of Medical Science, October 2010.
- Byrne J. Periconceptional folic acid prevents miscarriage in Irish families with neural tube defects. Accepted for publication, Irish Journal of Medical Science, October 2010.
- Cruz L, et al. Characteristics of HIV Infected Adolescents in Latin America: Results from the NISDI Pediatric Study. epub Journal of Tropical Pediatrics. July, 2010.
- Green D, Kawashima T, Stovall M, Leisenring W, Sklar C, Mertens AC, Donaldson AD, Byrne J, Robison LL. Fertility of male survivors of childhood cancer. A report from the Childhood Cancer Survivor Study. Journal of Clinical Oncology. 2010 Jan 10;28(2):332-9.
http://www.ncbi.nlm.nih.gov/pubmed/19364965?ordinalpos=18&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_Results_Panel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum