Second International Childhood Cancer Cohort Consortium Workshop
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Welcome

Terry Dwyer, M.D., M.P.H., Tasmanian Infant Health Study, Murdoch Childrens Research Institute (MCRI), Australia

Dr. Dwyer welcomed the participants to the second International Childhood Cancer Cohort Consortium (I4C) meeting. Attendees included representatives of participating cohorts, scientists working on hypotheses of potential interest to the consortium, and members of the Steering Committee appointed at the consortium meeting in 2005.

The purpose of the consortium is the prevention of childhood cancer using evidence from prospective children's cohort studies around the world. The consortium is needed to obtain the required prospective data because no single childhood cohort is large enough to have the statistical power to test key hypotheses alone. The I4C is focused on obtaining evidence that is likely to be more valid when obtained from a cohort study than from a retrospective case-control study. Medical research has contributed greatly to improved treatment outcomes for childhood cancer. However, little progress has been made in prevention of childhood cancer. Cancer remains the second leading cause of death in children 5–14 years of age. Retrospective case-control studies have been the principal strategy to examine the association of environmental exposures with childhood cancer. This strategy has yielded little progress in finding preventable causes. Recall bias may be an important factor. In addition, case-control studies do not permit measurement of relevant biologic factors prior to disease occurrence. Cohort studies can overcome the deficiencies of case-control studies, but cohort studies need to be very large for rare diseases such as childhood cancer. A study with adequate power to investigate childhood cancers such as acute lymphoblastic leukemia (ALL) would require about 1 million subjects.

Since it was proposed in 2004, the I4C has progressed steadily. The study now has 11 participating cohorts from 9 countries with about 999,500 subjects. The first meeting of investigators was held in September 2005 in Rockville, MD, USA. Testing of first hypotheses with pooled data will begin in 2008. A Steering Committee consisting of representatives of

[1] The National Children's Study is led by a consortium of federal agency partners: the U.S. Department of Health and Human Services (DHHS; including the National Institute of Child Health and Human Development [NICHD] and the National Institute of Environmental Health Sciences [NIEHS], two parts of the National Institutes of Health [NIH], and the Centers for Disease Control and Prevention [CDC]) and the U.S. Environmental Protection Agency (EPA).

cohorts and of funding institutions (NIH and EPA) has been established to develop policies and guidelines, organize meetings, promote the study, and coordinate data pooling and hypothesis testing. A paper describing the consortium was published in 2007: Cohort profile: The International Childhood Cancer Cohort Consortium (I4C). Rebecca C. Brown, Terence Dwyer, Carol Kasten, Danuta M. Krotoski, Li Zhu, Martha S. Linet, Jørn Olsen, Peter C. Scheidt, and Deborah M. Winn; for the International Childhood Cancer Cohort Consortium (I4C). *International Journal of Epidemiology* 36(4):724-730. (Available online at: http://ije.oxfordjournals.org/cgi/reprint/36/4/724).

Avon Longitudinal Study of Parents and Children (ALSPAC) Update

Jean Golding, Ph.D., Sc.D., Professor, Department of Community Based Medicine, University of Bristol, UK

Dr. Golding provided an overview of ALSPAC—also known as Children of the 90s. The study's overall objective is to understand the ways in which the physical and social environment interact, over time, with genetic inheritance to affect health, behavior and development in children and then into adulthood. Subjects were recruited from 1990 to 1992. Cohort inclusion criteria were pregnant women who resided in the geographical area of Avon, UK, with an estimated delivery date of April 1, 1991, through December 31, 1992. The study enrolled 14,541 (about 85 percent of the total eligible) pregnant women. There were 740 abortions/deaths. The study is currently following 13,801 mothers and 13,971 children.

ALSPAC data were collected using several methods: self-completion questionnaires, health records, biologic samples, environmental monitoring, education records, and hands-on assessments. Data collection has been successful: 3.5 years after delivery, about 80 percent of mothers are still responding. Biologic samples included maternal blood and urine during pregnancy; umbilical cord blood and slices; placentas; children's teeth, hair, and nail clippings; and children's blood and urine. DNA has been extracted from maternal and child blood samples. ALSPAC will be linked to the National Cancer Registry by January 2008.

The National Children's Study: The Big and the Thick of It

Peter C. Scheidt, M.D., M.P.H., Director, National Children's Study, NICHD, NIH, DHHS, USA

Dr. Scheidt described the important concepts of the Study: It is hypothesis-driven; exposure will begin with pregnancy; it will enroll 100,000 subjects; it has enough statistical power to study high-priority conditions; it includes gene-environment interactions; it involves a consortium of federal agencies as well as public-private partnerships; and it will serve as a national resource for future studies.

The five domains of priority exposures are physical environment, chemical exposure, biologic environment, genetics, and the psychosocial milieu. The five domains of priority health outcomes are pregnancy outcomes, neurodevelopment and behavior, injury, asthma, and obesity and physical development. The Study will be implemented at 105 locations. Contracts for seven Vanguard Centers were awarded in 2005. Contracts for 15–20 Study Centers will be awarded in fall 2007.

Eleven visits are scheduled as part of the core protocol. Women with a high probability of pregnancy will have one face-to-face visit and a follow-up telephone interview. Visits in a clinical setting will be during the second and third trimesters, at delivery, and at 3, 5, 12, and 20 years of age. Home visits are scheduled for the first trimester and at age 6 months, 12 months, 8 years, and 16 years. Contact between face-to-face visits will include telephone interviews, online communications, and mail-in questionnaires.

The Study will recruit women from preconception to early pregnancy. About 25 percent of the participants will enroll before conception; and about 90 percent will enroll within the first trimester. The goal is to recruit a sufficient number of women to yield 250 live births per year and have statistically valid representation of the targeted areas. In addition, the Study will include diverse populations by ethnicity, socioeconomic status, and family structure. Data will be collected during in-person home and clinic-based visits. Telephone interviews, computer contact, and mail-in questionnaires will be used between face-to-face visits. Data will include (1) psychosocial, demographic, neurodevelopmental, neighborhood, and contextual information; (2) biologic samples from mother, father, and child; and (3) environmental samples (air, water, soil, dust) from the child's environment (home, school, day care). For its first year of implementation, the Study was funded for the full amount requested. Funding for the second year is pending.

Babies in Bradford Study (BiB) Update

Richard Kwok, Ph.D., Epidemiologist, Environmental Epidemiology and Statistics Program, RTI International, USA

On behalf of John Wright, Director, Bradford Institute of Health Research at the Bradford Royal Infirmary, Dr. Kwok provided an update of BiB. BiB is a multiethnic, longitudinal birth cohort study to determine the differences in fetal growth and birth weight and the incidence, causes, and predictive factors of adverse birth outcomes and congenital abnormalities. The study will look at factors such as diet, housing, air quality, and exposure to different chemicals and toxins. Potential causes of premature birth, low birth weight, childhood cancer, heart and kidney disease, diabetes, and the impact of diet on genes and of bottle feeding on obesity will be investigated.

About 20 percent of Bradford's 380,000 residents originate from South Asia (India, Pakistan, and Bangladesh). There are about 5,500 births each year in the city; about 50 percent of the babies are born to parents of South Asian origin. The city has a high rate of consanguineous marriages and a high rate of socioeconomic deprivation within the ethnic and minority populations. BiB will recruit a multiethnic cohort of babies born in Bradford to investigate fetal growth and long-term outcomes by ethnic group. Accrual of samples will begin in July 2007. To date, more than 1,400 mothers have consented to participate.

Norwegian Mother and Child Cohort Study (MoBa) Study Update

Richard Kwok, Ph.D., Epidemiologist, Environmental Epidemiology and Statistics Program, RTI International, USA

On behalf of Andrej Grjibovski, M.D., Ph.D., of the Norwegian Institute of Public Health, Dr. Kwok provided an update on MoBa. The aim of MoBa is to quantify the influence of various social, genetic, nutritional, and environmental exposures on pregnancy outcomes and child

health. A questionnaire on maternal and child health status is sent to the mother at about 15 weeks of pregnancy and when the child is 6 months, 18 months, and 6 years old. Blood and urine samples from women are taken at the same time as the ultrasound examination. More than 90 percent of fathers accompany their partners to the examination, at which time the fathers are asked to participate in MoBa. If the father agrees, a blood sample is taken, and he is given a short questionnaire on his health status, medication, and occupational exposures. At birth, blood samples are collected from the umbilical cord and mother. Health outcomes are collected from hospital discharge registries, as well as other registries such as the medical birth registry, the cancer registry, and the diabetes registry. All blood samples are sent to the National Institute of Public Health in Oslo, where a biobank is organized for the storing and processing of all samples. As of June 2007, 77,406 women and 88,318 pregnancies have been recruited. Altogether, 78,778 births were registered by June 2007. Recruitment will continue until 100,000 participants have been enrolled. Questionnaires will be sent to the parents when the children are 6, 18, 36, and 72 months old. All cancer cases can be identified by linking the MoBa data to the nationwide cancer registry. Several MoBa papers, primarily about dietary data, were published in June 2007.

China Children and Families Cohort Study (CFCS): Progress Report

Li Zhu, M.D., M.P.H., Peking University Health Science Center, People's Republic of China

Dr. Zhu reported on CFCS. The study has been implemented in 37 counties and cities in four provinces (Hebei, Shanxi, Jiangsu, and Zhejiang). Two of these provinces surround Beijing, and two surround Shanghai. The foundation for CFCS began in 1991 when Chinese investigators began collaboration with CDC on the Neural Tube Defect Prevention Trial. The study areas have a total population of 20 million, with 150,000–170,000 newly married couples per year and 170,000–200,000 births per year. Enrollment of newly married couples and new births for the Neural Tube Defect Prevention Trial has continued since 1992. Total enrollment is now about 2 million. CFCS, a new cohort study, will enroll 300,000 couples within 3 years from preconception care. The study will also recruit grandparents. The study will follow children and their families for 20 years—a total of 6 million person-years from birth to 21 years. CFCS and other Chinese cohort studies rely on the infrastructure of the Family Health Surveillance System. Dr. Zhu provided a brief overview of the system, describing its four health care programs.

Childhood Cancer Etiology: Overview of Descriptive Patterns, Risk Factors, Power, and Cohort Consortium Logistics

Martha S. Linet, M.D., M.P.H., Chief, Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute (NCI), NIH, DHHS, USA

Dr. Linet discussed the etiology of childhood cancer. Childhood cancer accounts for 1–2 percent of total cancer burden. It ranks high as a cause of death in children. It differs from adult cancers in that it is derived mostly from nonepithelial tissues and is defined primarily by histologic and molecular features rather than anatomic site of origin.

The International Classification of Childhood Cancer (3rd edition, 2005) describes 12 categories of childhood cancer:

- Leukemias, myeloproliferative, and myelodysplastic neoplasms

- Lymphomas and reticuloendothelial neoplasms
- Central nervous system (CNS), other intracranial, and intraspinal tumors
- Neuroblastomas and other peripheral nervous cell tumors
- Retinoblastoma
- Renal tumors
- Hepatic tumors
- Malignant bone tumors
- Soft tissue and other extraosseous sarcomas
- Germ cell, trophoblastic, and other gonadal tumors
- Other malignant epithelial neoplasms and malignant melanomas
- Other and unspecified malignant neoplasms.

In the United States, 10,400 new incident cases and 1,545 deaths from childhood cancer are estimated for 2007. This compares with more than 1.44 million incident cancer cases in adults and more than 559,000 deaths that are estimated to occur in 2007. Thus, childhood cancer is rare. The most frequently occurring childhood cancers are leukemias (30.0 percent), CNS tumors (22.3 percent), neuroblastoma (7.3 percent), non-Hodgkin lymphoma (4.5 percent), and Hodgkin lymphoma (3.5 percent). Five-year survival has improved to the current rate of about 80 percent, but survival varies by type of cancer. Childhood cancer characteristics vary by age, gender, race, and ethnic group. During infancy, neuroblastoma, leukemia, CNS tumors, and retinoblastoma are more common. During adolescence, Hodgkin lymphoma, germ cell tumors, osteosarcoma, CNS tumors, and malignant melanoma are more common. Males have a notable predominance of lymphoma. Females have a predominance of thyroid cancer and malignant melanoma. Caucasians have a predominance of Ewing's sarcoma and ALL. African Americans have a predominance of Wilms' tumor and retinoblastoma. Africans have a predominance of endemic Burkitt's lymphoma and retinoblastoma. There is international variation in the rates of leukemia, brain/CNS tumors, Hodgkin lymphoma, bone tumors, and most other pediatric tumors. Within populations, there may be ethnic and racial variations in the rates of various malignancies. There may also be differences in age of certain childhood cancers among different countries.

The causes of childhood cancer are poorly understood. Geographic and ethnic differences can provide clues. Known risk factors include high-dose single ionizing radiation exposure, prenatal diagnostic radiation exposure (for example, "pelvimetry"), Down syndrome and other genetic disorders, and certain viruses (EBV and HIV). Putative etiologic agents include:

- High birth weight or very low birth weight
- Pesticides
- Parental occupational exposures
- Unknown infectious agents
- Diethylstilbestrol
- Maternal reproductive factors
- Maternal pregnancy diet, breastfeeding.

Because few exogenous risk factors have been established and causes are often considered as genetic, other endogenous, or "bad luck," quantification of international variation in childhood cancer may shed light on their etiology. An international study would consider descriptive patterns along with risk factors and could potentially generate data to assess likelihood of

nongenetic causes. One approach is to examine rate ratios (for example, ratio of highest to lowest incidence rates) and strict versus lenient rate ratios. Quantification of international variation would consider trend patterns and risk factor information.

The goals of the I4C are to advance understanding of the etiology and carcinogenic mechanisms in relation to childhood cancer. As the study moves forward, several important issues need to be addressed:

- Decisions on "exposures" and other variables available (for example, questionnaire data, biologic samples, measurement data)
- Strategies for following up children and assessing cancer outcomes
- Decisions on hypotheses to pursue. To these ends, the goals of this Workshop are to identify a few important hypotheses to evaluate, to establish working groups, and to make plans to conduct proof-of-principle initial collaborative efforts.

Discussion. Dr. Dwyer asked about the validity of comparisons of cancer rates among different countries. Dr. Linet explained that the validity has been improving as communication among international cancer registries has increased and as the proportion of categorization of cancer types as "other," "not otherwise specified," and "incompletely specified" has decreased in most registries. Complete ascertainment and population census data remain as issues. Robert Newton, Ph.D., commented the validity may depend on the particular region and particular country reporting the data. High mortality rates due to causes such as infection may, for example, reduce ascertainment rates for cancers such as leukemia. Because of uncertain validity, basing hypotheses on international variations in childhood cancer rates may be inappropriate.

Cohort Data Collection: Variables and Timing

Richard Kwok, Ph.D., Epidemiologist, Environmental Epidemiology and Statistics Program, RTI International, USA

Dr. Kwok provided an overview of the I4C participating cohorts, steps for data compilation, data domains, timing of data collection, and case ascertainment. The I4C combines prospective cohort studies from around the world to investigate birth outcomes, with follow-up through childhood. Key exposures relevant to childhood leukemia will be collected through questionnaire data and biospecimens. Participating I4C cohorts and the anticipated number of subjects are as follows:

Avon Longitudinal Study of Parents and Children (ALSPAC; UK)	14,062
Born in Bradford Study (BIB; UK)	10,000*
China Children and Families Cohort Study (CCFC; China)	300,000*
China–U.S. Collaborative Project on Birth Defects and Disabilities Prevention (CPBDDP; China)	247,831
Danish National Birth Cohort (DNBC; Denmark)	101,042
French Study on Environment and Children's Health (ELFE)	20,000*
Infancia y Medio Ambiente (INMA; Spain)	3,500*
Jerusalem Perinatal Study (Israel)	92,408
Norwegian Mother and Child Cohort Study (MoBa; Norway)	100,000*
National Children's Study (NCS; USA)	100,000*
Tasmanian Infant Health Survey (THIS; Australia)	10,627

*These are target numbers of children to be enrolled

The purpose of compiling cohort data is to determine which types of data are most reliable to pool. There are several steps for compiling I4C data. Information from cohorts will be collected from publications, questionnaires (if available), protocols (if available), and a data dictionary (if available). The information will be abstracted; key domains, data collection sources, and time points will be identified. Domains and questionnaires will then be compared. Data compilation will allow recommendations for (1) pooled analysis of existing studies or (2) new data collection efforts for future studies (future pooling).

Antenatal priority domains of interest for I4C outcomes are occupation/type of work, smoking/drug use (mother, father, passive (maternal)), diet (fish, seafood, yogurt), radiation exposure, pesticide/chemical exposure, maternal infection, sun exposure/vitamin D, supplements during pregnancy, and folate intake. Biologic specimens including but not limited to maternal blood are another domain of interest. For children, postnatal priority domains include:

- Anthropometry
- Infections up to 1 year
- Radiation exposure
- Pesticide/chemical exposure
- Feeding habits
- Mixing with others
- Sun exposure
- Fish intake
- Yogurt intake
- Passive smoking
- Atopy/asthma.

Data on maternal and paternal occupation/type of work, smoking, and atopy/asthma will be compiled and analyzed, as will data on biologic specimens such as neonatal dried blood spots and cord blood collected from the children. Dr. Kwok presented and discussed the following:

- Data collection of selected domains during pregnancy by cohort
- Data collection of selected domains during infancy (first year) by cohort
- Collection of biologic specimens during pregnancy by cohort (samples from mother)
- Collection of biologic specimens during infancy (first year) by cohort (samples from child).

There are two resources for data pooling: (1) an Excel spreadsheet detailing available questionnaire information by domain, study subject, and time period compiled by MCRI and RTI International staff in July 2007, and (2) a document containing domains along with relevant studies examining the validity and reliability of these measures compared to a gold standard, compiled through a literature review conducted by MCRI and RTI International staff in July 2006.

Cases of childhood cancer were ascertained as follows:

- E-mail survey of I4C cohorts conducted on August 1, 2007
- Information obtained from 6 of the 11 cohorts to date
- Total number of childhood cancers (ALL, acute myeloid leukemia, and other leukemias)

- Case ascertainment systems (for example, registries, parent reports, and clinical follow-up of cohort members).

The next steps for cohort data collection are to finalize policies and procedures and membership guidelines and further discuss data pooling.

Discussion. Kjeld Schmiegelow, M.D., Dr.Med.Sci., asked whether information was available on which type of biologic material is stored and how rapidly after birth it was processed. Dr. Kwok replied that some of this information has been gathered from published sources. MoBa investigators provided the most detailed information on biologic materials. Information from other cohorts is being compiled. Tom O'Dowd asked whether information on alcohol consumption had been collected. Dr. Kwok noted that such information has been collected by most of the cohorts. Jørn Olsen, M.D., Ph.D., suggested that information on the number exposed be added. Dr. Olson asked whether a committee could examine the quality of diagnosing across the cohorts. Dr. Kwok agreed that analyzing the quality of the data is important.

I4C Policies and Procedures Manual

Carol Kasten, M.D., Geneticist and Medical Officer, Epidemiology and Genetics Research Program, NCI, NIH, DHHS, USA

Dr. Kasten familiarized attendees with the draft policies and procedures manual. She proposed that I4C investigators resolve authorship guidelines early. The guidelines should be individually accepted by the cohorts through membership agreements. It was acknowledged that ethical, legal, and social issues related to data pooling across cohorts of children could not be resolved at this meeting.

The policies and procedures manual was first discussed by the I4C Steering Committee, which convened after the September 2005 meeting in Bethesda, MD, USA. The Steering Committee consists of representatives of cohorts and funding institutions such as NIH, EPA, and MCRI. The manual will be developed by I4C committees (publications, writing, analysis, statistic, other), the Steering Committee, outside institutions (for example, NCI, NICHD, EPA, MCRI), the advisory committee, and member cohorts. Dr. Kasten suggested that the advisory committee be somewhat independent of the I4C so it can provide unbiased opinions and suggestions.

The I4C's mission is to collaborate among international cohorts to investigate the role of environmental exposures and genetic susceptibility in the etiology of childhood cancer via pooling of individual cohort data sets to improve power to study rare diseases.

The I4C Steering Committee has several functions:
- Develop the I4C policies and procedures manual for data collection, collation, management, and quality control
- Maintain the I4C Web portal
- Develop and maintain databases
- Establish criteria for review, selection, and prioritization of research proposals using I4C cohort data or I4C resources
- Develop standard variables for analysis across cohorts

- Coordinate protocol development for selected hypotheses
- Conduct outreach to additional ongoing proposed cohorts.

The policies and procedures manual specifies the following criteria for I4C membership:
- Large-scale prospective cohort studies of environmental effects on children's health collecting data no later than 1 month after birth
- Data collection of one or more of the following types:
  - Biologic samples from mother and child
  - Environmental samples
  - Dietary samples
  - Questionnaire or measurement-derived covariate information
- Outcome data pertaining to child cancer.

The guidelines for I4C authorship will be inclusive rather than exclusive. In general, authorship should meet the International Committee of Medical Journal Editors (ICMJE) definition:

> "A test to help determine whether a center should be included in the author list is 'could the work have been completed without the center?' If not, then each center that provided data should be represented in the authorship."

The draft policies and procedures manual outlines data sharing and publication policies, defines intellectual property, and addresses some process issues such as comparability of questionnaires, domains, and availability of biospecimens. Other processes such as data access and availability, data pooling and processing, and reporting results remain to be discussed and agreed upon.

Discussion. Dr. Linet clarified (1) that reference to "environmental factors" should be "exogenous factors" and (2) that the Steering Committee would be an evolving group but with equitable and representative membership. Dr. Olsen suggested that a person from the European Union (EU) serve as a Steering Committee member. He cited several reasons for EU involvement in the I4C. He proposed time limits on the use of requested data; data cannot be "reserved" too long in advance of analysis and publication. Silvia R. Brandalise, M.D., asked about the timing of questionnaires, that is, at 1 month versus 4 months. Dr. Dwyer replied that timing would depend on the hypothesis being tested and whether there was a critical period of data collection. Dr. Scheidt commented that advisory committees can be expensive and time consuming. The I4C may not need a separate, overarching advisory committee; each cohort may have its own advisory committee. Dr. Scheidt noted that the Web portal can be an increasingly useful tool. Rebecca C. Brown, M.P.H., M.E.M., will set up Web portal accounts for I4C participants. Dr. Dwyer commented that, although there were no problems in transmitting de-identified data, insufficient personnel/staffing hindered his cohort/institute from providing data to Dr. Kwok in a timely manner. This issue relates to access of I4C data and is impacted by lack of adequate funding. Nancy Potischman, Ph.D., asked whether the draft I4C policies and procedures manual was based on what is being done by other U.S. cohort consortiums (for example, advisory committee, authorship rules). Dr. Kasten explained that the I4C policies are informal and unstructured. Statements on authorship guidelines and publications polices were helpful.

Chromosomal Translocations and Hyperdiploidy at Birth

Joseph Wiemels, Ph.D., Associate Professor, Department of Epidemiology and Biostatistics, University of California, San Francisco, USA

Investigating hypotheses about chromosomal translocations may be a productive venture for the I4C. To this end, Dr. Wiemels reviewed chromosomal translocations and hyperdiploidy at birth in relation to leukemia etiology. There are six molecular genetic subsets of ALL in children 1–8 years old: *TEL-AML1*, hyperdiploid, *E2A-PBX1*, *MLL/11q23*, *BCR-ABL*, and "other." *TEL-AML1* translocations account for about 25 percent of ALL cases in children. Hyperdiploid leukemias account for another 25 percent. Hyperdiploidy is characterized by at least five extra chromosomes, which typically include 21, X, 10, and 14. *TEL-AML1* translocations and hyperdiploidy account for most cases of ALL in children 2–6 years old.

In the current etiological model, childhood leukemia is a disease caused by at least two genetic mutations (called "hit 1" and "hit 2"). These mutations will occur in clonal succession at different periods in development. The hits may be dependent on or independent of each other. One hit generally occurs before birth. Mutations can help investigators learn about leukemia etiology. Tracking mutations can be used to understand when leukemia originates, and mutation mechanisms can help show how leukemia occurs.

Dr. Wiemels reviewed anatomy and timing of *TEL-AML1* translocations, discussed possible postnatal events leading to "hit 2," presented a two-step model for the natural history of cALL, and summarized the timing of pediatric leukemia genetics. Studies of several populations have shown that the *TEL-AML1* translocation is necessary but not sufficient for *TEL-AML1+* leukemia. About 1 percent of normal-born children are positive for *TEL-AML1*, yet only 1 of 2,000 children will get *TEL-AML1+* leukemia.

Data from several international studies indicate geographical variations in frequency of *TEL-AML1* translocation among B-lineage ALL. Dr. Wiemels posed two hypotheses on the meaning of different translocation rates: (1) Translocations occur at different rates *in utero* in different populations, and (2) translocations occur at similar rates but induction of secondary events is different. Cord blood screening could help answer a number of questions about population rates of mutation markers, relative leukemia rates between countries and populations, pregnancy-associated epidemiologic determinants for the presence of mutations, leukemia rates among those children who are positive for translocation/mutation markers at birth, and epidemiologic differences among those who have translocations and progress to leukemia versus those who do not.

Cord blood is the perfect material for chemical testing for pregnancy exposures. Volatile and unstable compounds can be assessed by screening cord blood, and electrophilic compounds can be assessed as albumin adducts. Cord blood and neonatal screening could be used to identify those children who experience a "first hit." Identification of epidemiologic determinants of the prenatal mutation, and the conversion to leukemia, could lead toward prevention. Only through large cohort studies can the epidemiology of the first hit be studied. One goal of translocation studies is to develop a leukemia vaccine.

Hyperdiploidy occurs in about 35 percent of childhood lymphocytic leukemias. Hyperdiploidy occurs in one specific catastrophic event and occurs prenatally. Although a specific marker has been identified, a procedure for screening cord blood or neonatal blood spots has not been developed. A backtracking procedure could be used to study high hyperdiploidy. The first step would be to clone the immunoglobulin (IGH) gene, which is a specific marker in every B-cell. This marker would be used to screen cord blood or neonatal blood spots for *RAS* mutations, which are present in 40 percent of lymphocytic leukemia cases.

Dr. Wiemels presented data on the increased risk to childhood leukemia due to prenatal pesticide exposure. Only children that have pesticide exposure before birth, or both before and after birth, have increased risk. Exposure after birth does not lead to a statistically significant increase in risk. Cord blood can be collected, stored, and later screened for pesticides. Cord blood is a perfect material for chemical testing for pregnancy exposures. Volatile and unstable compounds can be assessed. Electrophilic compounds can be assessed as albumin adducts.

Discussion. In response to a question from Dr. Zhu, Dr. Wiemels explained that although *TEL-AML+* translocations can be detected at birth, it cannot be predicted from cord blood screening which *TEL-AML+* children will subsequently be diagnosed with leukemia. Even after children are treated and cured of leukemia, they remain *TEL-AML+*. Not all children who are diagnosed with leukemia are *TEL-AML+*. Dr. Wiemels suggested that I4C screen for both *TEL-AML* and *AML1-ETO* translocations. Dr. Schmiegelow commented that, because of RNA instability, cord blood cells should ideally be processed within 24 hours of collection (but no later than 48 hours after collection) to screen for leukemia molecular genetic subsets. The I4C would benefit from quality control studies of cord blood collection and processing. DNA is relatively stable once stored, but RNA—which is essential to studying molecular genetic subsets—is not stable. RNA stabilizers can be used. Ethical issues of detecting leukemia-related translocations at birth were briefly discussed.

Paternal Age

Jørn Olsen, M.D., Ph.D., Professor and Chair, Department of Epidemiology, University of California, Los Angeles, USA

Dr. Olson discussed paternal age and childhood cancers. Increasing paternal age is associated with a large number of reproductive failures and diseases with an onset later in life. The increasing number of mutations in the male germ cell line has led to a number of studies on the association between paternal age and reproductive failures/diseases with a later onset. These studies have shown associations between paternal age and:

- Spontaneous abortions
- Some congenital malformations
- Preterm birth
- Low birth weight
- Perinatal and infant mortality
- Epilepsy
- Schizophrenia
- Some childhood cancers.

In theory, the number of (premeiotic) mitotic cell divisions during spermatogenesis and their remarkable increase with aging compared with oogenesis favor genetic risks for the offspring of older men. Although numerical and structural chromosomal anomalies are known, an influence of paternal age on genetic risks for offspring has not been found. However, in several autosomal dominant disorders affecting three specific genes (fibroblast growth factor receptors 2 and 3, RET proto-oncogene), the risk for a child to be affected increases with paternal age at time of birth. A number of studies have shown an association between paternal age and childhood cancer.

Age effects may be due to biologic aging, cumulative environmental exposures, or confounding/bias. Isolating the effect of paternal age from an effect of maternal age is difficult because the two ages are often closely correlated. Most information will come from parents with a large variation in age, but parents with a large variation in age are not randomly selected from all parents.

The I4C can use cohort data to examine differences in lifestyles (and mutations), infections, and medicine use in couples with large variations in age. In concluding, Dr. Olson presented a flowchart of the study population from the DNBC, and he presented information on characteristics—such as smoking, alcohol consumption, body mass index, and social status—related to maternal and paternal ages and age differences.

Discussion. Dr. Dwyer asked whether the preliminary data suggest that the I4C will have a positive finding or whether it is more likely the study will gather better data showing that paternal age is not important. Dr. Olsen replied that there are good reasons to think that childhood cancers are candidates for something that would correlate with paternal age and the increasing rate of mutation in particular cell lines. The limited available information does not support the correlation, but the finding could be confounded by other factors. A strong association is not expected. A moderate association is more likely. Sharon Savage, M.D., explained that her research focuses on telomere biology and genes that are important to telomeres. Telomeres are at the ends of chromosomes and are critical for maintaining chromosome stability. Telomeres shorten with age. In addition, telomere length is inherited. The association of telomeres and childhood cancer would be an interesting area to investigate in I4C.

Pesticides

Joachim Schüz, Ph.D., Head, Department of Biostatistics and Epidemiology, Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark

Dr. Schüz provided an overview of pesticides and childhood cancers. Carcinogenicity of pesticides has been demonstrated in bioassays. There are both potential genotoxic and nongenotoxic mechanisms. According to the International Agency for Research on Cancer (IARC), more than 25 Group I pesticides are carcinogenic to humans—some of them are still registered and applied in various countries. There are numerous sources of pesticide exposure:

- Indoor insecticides with persistent household contamination
- Private and public lawn and garden use
- Agricultural application drift; dust tracked into homes
- Leak, spills, and accidents during manufacturing

- Contamination of groundwater, food, breast milk
- Applications on pets
- Preconceptional or *in utero* exposures.

The majority of case-control studies have shown an association between pesticide exposure and childhood cancer. Stronger associations have been shown with indoor exposures. Epidemiological evidence supports the biologic plausibility of these associations due to the carcinogenicity of pesticides in animal studies. In addition, children are considered more vulnerable due to immature metabolism and higher intake of pesticides by unit of body mass compared with adults. However, the few cohort studies conducted have shown no or weaker associations than case-control studies. Case-control studies are prone to bias, use crude exposure assessments, and have internal inconsistencies such as lack of dose-response effects and homogeneous patterns. There are limitations to retrospective epidemiological studies, including selection bias, difficulties remembering past events, lack of agreement between exposure metrics, exposure misclassification, and level of detail in recall (for example, brand names are difficult to remember). Bias may be introduced because of level of education or age at diagnosis.

Dr. Schüz presented data from six new studies that identified high-exposure groups, refined geographic information system methods, minimized recall bias, and combined objective exposure measurements with questionnaire data. These studies emphasized the importance of avoiding heterogeneous case groups, timing of exposure, substance-specific investigations, and quantitative dose estimation.

Epidemiological studies suggest an overall weak-to-moderate association with various childhood cancers, but this association may be considerably stronger in subgroups. Because childhood cancers are rare diseases, crude categorizations are unlikely to reveal entirely new insight. Determining associations between pesticide exposure and childhood cancer is prone to case-response bias. Prospective questioning in cohort studies can be expected to avoid differential reporting bias. Improved methodology in such prospective studies include more universally understandable screening questions, nested case-control studies with an optimization of statistical power using a counter-matched design, and identification of possibly more relevant exposures with respect to substances, dose and timing of exposure.

Studying the association between pesticide exposure and childhood cancer is relevant because pesticide use is common in many regions of the world. Epidemiological studies suggest an overall weak-to-moderate association with various childhood cancers, but this may be considerably stronger in subgroups. Truly relevant exposure—including dose, timing, and substance—needs to be determined. Improved methods are now available to conduct such studies. The I4C may offer a unique opportunity to investigate the association of pesticide exposures and childhood cancer.

Discussion. Dr. Golding commented that the ALSPAC study inquired about pesticide exposure early in pregnancy. In-home visits revealed differences in self-report exposure and materials that were used in the homes and were, in fact, pesticides. Many mothers often did not know what materials were pesticides and did not accurately recall use. The design of questionnaires is very important in studying pesticide exposures. Dr. Golding asked whether biospecimens would

provide better evidence of exposure. Dr. Newton noted that pesticide exposure may not be all bad. For example, widespread use of DDT in Africa to kill malaria-carrying mosquitos led to the reduction in the incidence of Burkitt's lymphoma. Several case-control studies suggest the use of household pesticides in Africa reduces the risk of Burkitt's lymphoma. Dr. Kwok asked about the metabolism of pesticides, the duration of exposures, and the timing of collection of biospecimens. Elisabeth E. Knudsen, Ph.D., explained that "pesticides" is a broad category of compounds. The collection of biospecimens (for example, from urine or blood) depends on the specific compound of interest. Jacqueline Clavel, Ph.D., commented that biospecimens should be collected at more than one time point. Dr. Olson asked Dr. Schüz about studies on perfluorinated compounds. There is evidence that these compounds impair fetal growth and may play a role in congenital malformations. Dr. Scheidt commented that, with regard to proof of concept, studies might best be limited to one or two persistent pesticides and include biospecimens. Such studies would focus on one or two hypotheses. Dr. Clavel noted that insecticides are often used to control head lice in children. Information on this topic should be included in questionnaires.

Infection and Childhood Leukemia

Eve Roman, Ph.D., Professor of Epidemiology, Department of Health Sciences, University of York, UK

Dr. Roman noted that about one in five of all cancers has a recognized infectious aspect to its etiology. She reviewed some of the early literature on infection and acute leukemia in children and presented United Kingdom Childhood Cancer Study (UKCCS) data on ALL and prior infectious illness in children. In 1917, Ward investigated the association of infection and acute leukemia, concluding that it was not an infectious disease but possibly a metabolic disorder. In 1942, acute infections were suggested as a possible etiological factor because some acute infections frequently preceded the development of acute leukemia. Between 1988 and 1990, investigators suggested that population mixing played a role in the etiology of acute leukemia and Greaves proposed the "two-hit hypothesis" for ALL, speculating that the common subset of ALL peaking in children 2–5 years old may develop in response to infection in children who have been underexposed to common microorganism(s) in infancy. Further evidence for infective associations of childhood leukemia led Smith in 1997 to hypothesize:

> "The etiologic agent [that] causes a primary infection in the mother is transmitted to the fetus, and as a consequence of this in utero infection, the child is at increased risk of developing acute lymphoblastic leukemia before the age of 5."

The UKCCS looked at children 15 years of age or younger who were registered for primary care with a general practitioner. Leukemia cases were ascertained from multiple sources and compared with controls who were selected from primary care population registers and individually matched to cases on date of birth, sex, and region of residence.

Compared with controls, case children with ALL (2–5 years of age) had more episodes of infectious illness. Excess infectious illness was apparent from birth, and there was no obvious specificity. Within the case series, children with more infections tended to be diagnosed with leukemia earlier. The following was concluded from the UKCCS data:

- From birth onward, children who develop ALL have more (not fewer) infectious illness

episodes that those who do not.
- The difference appears most marked in those exposed to infectious challenge from other children.
- ALL risk does not vary with birth order.
- ALL risk does not vary with deprivation/social class.

Discussion. Dr. Linet described the UKCCS as the only major case-control study that used records from primary care general practitioners. This approach was considered for the U.S. case-control study, but it was not feasible due to high costs. The ALL cases do not have serious infections such as those that might be seen with immunodeficiency disorders. Because children diagnosed with ALL are infected with common microorganisms but at a higher rate, a mild immunodeficiency disorder may be involved. Cohort studies would be able to explore this possibility. David Martin, M.D., asked whether the parents of children with ALL are more likely to seek medical care when their child has an infection. There may be parental selection for which infections will need medical attention. In addition, a child brought to a physician will be most likely be diagnosed with some type of infection. Dr. Roman explained that in the analysis presented children with higher rates of infection during their first year of life were not actually diagnosed with ALL until they were between 2–5 years old. Dr. Golding asked whether UKCCS examined medications prescribed during doctor visits. During the first year of life particularly, children are prescribed antibiotics at high rates. Dr. Roman said data on antibiotics and other drugs were currently being investigated. Mr. O'Dowd asked about fungal infections, most frequently oral candidiasis. Oral candidiasis is commonly associated with bottle feeding, which can serve as a confounder to studies of infection and childhood leukemia. Dr. Roman replied that this did not explain the results since most of the ALL cases with neonatal infections had been breast-fed. Dr. Schmiegelow commented that children with subacute leukemia—who have often been in the preleukemic phase for a while—respond well to treatment and subsequently feel much better. It is possible that preleukemic children may seek medical care more frequently than other children, and Dr Roman agreed but pointed out that it was only visits for infections that were elevated. Dr. Schmiegelow cited a Danish study that linked daycare attendance with the leukemia registry. Study results showed that the risk of leukemia was reduced by 40 percent for children who participate in daycare. The longer the children were in daycare, the lower their risk of leukemia. Linking attendance with registry records removes recall bias.

Birth Weight by Gestational Age

Joachim Schüz, Ph.D., Head, Department of Biostatistics and Epidemiology, Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark

Dr. Schüz discussed birth weight and its association with childhood cancers. There is a higher incidence of large-for-gestational-age births in Western societies. High birth weight has been associated with risk of several childhood cancers and adult cancers (for example, breast, prostate, colon). Low birth weight has been investigated in relation to maternal smoking and X-ray exposure, but the results have been inconsistent. Predictors of high birth weight include male gender, ethnicity, multiparity, gestational diabetes or hypertension, parental birth weight, birth weight of older siblings, maternal prepregnancy body mass index, and maternal weight gain during pregnancy.

Epidemiological studies have revealed some degree of consistency in the association between birth weight and leukemia, especially for ALL. For CNS tumors, the association is less clear, but there may be an association with astrocytoma. For Wilms' tumor, there is some degree of consistency, but it is suggested to be mainly due to a subgroup of patients with Beckwith-Wiedemann syndrome. There are fewer data for other childhood cancers.

Retrospective studies generally have bias problems with recall and subject selection. However, validation studies showed very good agreement between self-reports and obstetric records for birth weight. Results of interview-based studies and birth records-based studies seem to be comparable. Gestational age is, however, more difficult to remember. Retrospective studies also have bias problems with subject selection. For example, in a German case-control study, an underrepresentation of preterm babies was noticed. Questions remain about how to include gestational age in studies on birth weight and childhood cancer and one recent suggestion is to investigate birth-weight-by-gestational-age. Data suggests that both high birth weight and large-for-gestational-age (LGA) (also in normal birth weight babies) increase the risk of leukemia.

Possible mechanisms for the role of birth weight in childhood cancers include:
- High birth weight may result from high levels of growth factors, which may induce proliferative stress on bone marrow. One growth factor, IGF-I, is essential for somatic growth and plays a role in normal hematopoiesis. Another growth factor, IGF-II, is important in the regulation of cell proliferation.
- Bone marrow volume is correlated with fetus weight. Greater bone marrow volume results in higher number of cells prone to random genetic aberrations.
- In CNS tumors, regulators of embryonic brain development may remain upregulated in the presence of high IGF-I.

The following areas of investigation have been proposed:
- Disruption of genomic imprinting associated with overgrowth syndromes
- Growth-related genes including human leukocyte antigen-G, phosphoglucomutase, and peroxisome proliferator-activated receptor γ2
- Circulating levels of IGF-I
- Other factors such as sex-steroid hormones
- Genetic lesions at chromosome 11p15 with genes encoding IGF-II and Wilms' tumor.

Life Course Perspective

Nancy Potischman, Ph.D., Nutritional Epidemiologist, Office of the Associate Director of the Applied Research Program, NCI, NIH, DHHS

Dr. Potischman listed four life course perspectives on the relationships among risk factors:
- Critical periods (including programming): Adverse environmental exposures during rapid physical or developmental growth may lead to irreparable damage to structure and later function.
- Critical periods with later effect modifiers.
- Cumulative exposure: Long-term gradual damage to health results from various environmental or other insults; insults are independent and uncorrelated.
- Chains of risk: Accumulation of risk occurs where insults are correlated; one bad experience

leads to another.

In the life course approach, exposures occur any time during fetal life, childhood, adolescence, or later and can contribute to the outcomes. A longitudinal approach is the only way to address the relationships among risk factors and links with outcome. A variety of statistical approaches are being explored to promote this approach.

Prospective data for childhood cancers could include nested case-control data (for example, maternal and child blood specimens, pregnancy exposures, diet, and other questionnaire data), growth over time (for example, trajectories, timing of changes in growth, timing of attained landmarks), and better assessments of duration of exposure.

Dr. Potischman reviewed the findings from studies on birth weight and subsequent risk of breast cancer; growth patterns and breast cancer risk; birth weight and risk of breast cancer; birth weight, childhood growth, and risk of breast cancer; biologic correlates high body weight (normal weights for gestational ages); and determinants of birth weight.

With regard to pregnancy and prepregnancy diet, energy intake/energy balance will influence weight gain and potentially birth weight. Consumption of micronutrients may influence a variety of systems (for example, maternal marine fatty acid intake during pregnancy and IQ in offspring). Current recommendations for dietary intakes among obese people should be revisited. Data from animal models suggest possible dietary influences on childhood cancer. For example, environmental, particularly nutritional, manipulation leads to changes in DNA methylation. However, the relevance of these animal studies to *in vitro* fertilization, small for gestational age, and very premature children is not known. Candidate genes have been identified, which may have undergone epigenetic modification to alter growth and metabolism. These findings should be evaluated in other studies.

Issues to address in future studies include:
- Relationship between body composition of birth weight and later body mass index
- Whether higher birth weight is related to later lean mass and not fat mass
- Whether birth length is more important than birth weight for later outcomes
- Whether determinants of birth weight and composition differ across study populations
- Variation in risk related to hormonal and other biomarker differences across populations
- Assessing growth rate, height, timing of growth spurts, and attained adult height in relation to birth weight
- Assessing biomarkers in pregnancy in relation to later outcomes

Birth Defects and Childhood Cancer

Carol Kasten, M.D., Geneticist and Medical Officer, Epidemiology and Genetics Research Program, NCI, NIH, DHHS, USA

Dr. Kasten described the background on birth defects and childhood cancer and discussed several hereditary cancer syndromes. In 1964, Robert Miller described the relationship between aniridia and Wilms' tumor (WAGR syndrome). It is now recognized that several genetic syndromes characterized by birth defects are accompanied by cancer. Hereditary cancer syndromes include:

- Li–Fraumeni (p53)
- Wilms' tumor (WT1, others)
- Ataxia–telangiectasia (ATM1)
- Familial adenomatous polyposis (APC1)
- Cowden disease (PTEN).

Dr. Kasten characterized and compared some of the differences between expression in children and adults of Cowden disease, Proteus syndrome, Bannayan-Riley-Ruvalcaba syndrome, and Fanconi anemia. Newly identified cancer-associated birth defects include Hirschsprung's disease, cartilage-hair syndrome (RMRP), and Alagille syndrome.

There are several reasons to study birth defects. Identification of genetic etiology can reveal genetic and epigenetic mechanisms involved in carcinogenesis. Birth defects can be the "gene" in initial gene-environment studies of carcinogenesis. With regard to biologic plausibility, mutagens may be the "environment" in gene-environment studies. In addition, mutagens may be teratogens and carcinogens. Epidemiological studies have shown an increased hazard ratio for cancer among children with birth defects. Results from the Collaborative Perinatal Project showed that the presence of documented birthmarks (for example, hemangiomas, pigmented nevi, lymphangiomas, café au lait) significantly increased the risk of cancer. Birth defect registries such as the International Clearinghouse for Birth Defects Surveillance and Research in Finland may be able to provide data to the I4C.

The study of birth defects provides an opportunity to study gene-environment interactions. In studies such as the I4C, failure to track birth defects may confound data because known hereditary cancer syndromes will be included as "sporadic" cases of cancer. Childhood cancers may not be the result of the environment; they may be the result of genes. Failure to track birth defects will diminish the opportunity to contribute to other studies in children.

Recap of Day 1

Terry Dwyer, M.D., M.P.H., Tasmanian Infant Health Study, Murdoch Childrens Research Institute (MCRI), Australia

Dr. Dwyer summarized the issues discussed on Day 1 of the meeting:
- Rationale for a prospective cohort study of childhood cancer
- Recall bias
- Linking exposures to biologic intermediates
- Difficulty in recruiting representative control groups in case-control studies
- Availability of information/measurements of relevant domains from several cohorts
- Findings from case-control studies of childhood cancer.

Creation of a Data Dictionary and Core Protocols for Future Analyses

Richard Kwok, Ph.D., Epidemiologist, Environmental Epidemiology and Statistics Program, RTI International, USA

Dr. Kwok discussed the following topics:
- The possible collation of cohort materials

- The synthesis and derivation of merged variables, including use of existing data and external validation data
- Draft recommendations for future studies (for future pooling).

He reviewed the steps to compile data and the antenatal and postnatal priority domains for I4C outcomes (see Cohort Data Collection: Variables and Timing). Data pooling for the I4C is possible, but success of this effort depends on a variety of factors such as the complexity of questions and the wording of questionnaires and answers.

There is a spectrum of difficulty in data pooling. Standardized measures such as anthropometry, head circumference, length, and birth weight are simple to pool. It is more difficult to pool less standardized measures because of variations in the wording of questions and differences in study focus and study measures. The relative ease of pooling data for supplements and smoking is considered "medium difficult." Dr. Kwok discussed wording of existing questions, merged variables for existing data, and external validation and presented draft recommendations for new studies for supplements (folic acid) and smoking. The relative ease of pooling data on personal exposures such as pesticides, occupation, and type of work, and child infections is considered "difficult." Recommendations for new studies are as follows:

- Folic acid supplements
  - Collect details on frequency, dosage, and timing
  - Collect information more broadly on vitamins, minerals, or dietary supplements
- Maternal antenatal smoking
  - Collect details on dose of tobacco and time period of pregnancy
  - Careful definition of passive smoking is required
  - Collect biosamples, if possible
- Pesticides and occupation
  - Collect details on specific chemicals exposed during work and at home
  - Collect occupation/job title as a proxy for chemical exposure
  - Collect biosamples
- Child infections
  - Ask whether a child had an infection and, if so, age of onset of infection
  - Sensitivity to cultural interpretation of events (for example, rashes); need careful standardization of signs and symptoms of illness descriptions across countries
  - Collect detailed information at 1 and 6 months.

Dr. Kwok concluded that data pooling is feasible, but its success depends on a variety of factors, including the complexity of questions and the wording of questionnaires and answers.

Discussion. Dr. Olsen said the next step in the data pooling process is to determine whether any data are missing, how the data are coded, and the general quality of the data. He proposed a central repository for de-identified data sources. He commented on the challenges of ethical approval for pooled data analyses; the I4C will have to develop a mechanism to address this issue. Dr. Scheidt asked about challenges of translating questionnaires and answers and the impact of translations on data pooling efforts. Dr. Olson and Andrej Grjibovski, M.D., Ph.D., said neither the Danish nor Norwegian data used official English translations. These two studies have collaborated to harmonize their questionnaires and have prepared guidelines for using their

data. Dr. Dwyer commented that the next step for data pooling should be validation of the questionnaires in each study population. Issues regarding subject selection need to be explored. Richard W. Jones, D.Phil., Ch.B., M.B., suggested developing (1) mechanisms to ensure comparability and (2) quality assurance schemes for the different questionnaire-type measurements (for example, smoking). Tracy Lightfoot, Ph.D., asked how the investigators would take into account the issue of folic acid fortification/supplementation in the different countries. Dr. Potischman said the food composition data reflect folate fortification for the years when the questionnaires were administered. Using the food composition database for the appropriate years for the appropriate country provides acceptable information.

The Environment and Its Effects on Childhood: An International Core Study Protocol for a Longitudinal Survey

Jean Golding, Ph.D., D.Sc., Avon Longitudinal Study of Parents and Children, Professor, Department of Community Based Medicine, University of Bristol, UK

Dr. Golding discussed the development of an international core protocol to study effects of the environment on children. This protocol could be used in both developed and developing countries. Dr. Golding defined environment as the external factors influencing the life, development, and activities of people, plants, and animals. Environment includes chemical contaminants, socioeconomic environment, psychosocial influences, diet, and infectious agents. She discussed the rationales for health surveys and longitudinal studies and why studying the environment and genetic components are important. Dr. Golding listed the critical development periods for studying environmental exposures and health outcomes.

An important aspect of longitudinal studies is defining the study population. Representative populations, geographically defined populations, exclusion criteria, and organizational structure were mentioned. Data collection personnel and consistent adherence to the protocol are key issues. Other key issues include how to measure exposures, how to collect and store biospecimens, designing questionnaires, addressing ethical issues, and piloting and validating studies. Funding is another important aspect that must be considered. Elements of funding include accurate costing, writing grants, knowing who to approach and whether to include commercial companies, and setting up contracts. Positive relationships with potential study subjects should be developed when they are approached at enrollment, and the positive relationships need to be maintained to retain subjects and keep them committed to the study. There should also be positive relationships with local, national, and international media.

Collaboration with other scientists helps with contribution to finances and scientific output and with data ownership. Building in substudies can provide detailed validation studies as well as randomized controlled trials. Linkages with other databases include education, health records, GIS mapping, and census data. A centrally funded office is of vital importance for advice, assistance, training, ensuring comparability across studies, quality assurance, and providing a library of resources.

Discussion. Dr. Scheidt proposed making the protocol development document available on the Web portal. Dr. Golding said the document will be published as a supplement to the journal *Pediatric and Perinatal Epidemiologist*. It will be peer-reviewed before publication. Dr. Linet

asked how a centrally funded office could be realized. Dr. Krotoski noted that the World Health Organization (WHO) is unable to fund such an office. However, increasing focus on environmental health in developing countries—particularly the prevention of disabilities and long-term negative impacts on populations—will allow longitudinal studies to approach potential funding institutions such as the World Bank and Gates Foundation. Dr. Olson suggested that the term "data ownership" not be used in the protocol. Mr. O'Dowd said data from the Irish studies become part of the public archive and are accessible to researchers after a designated release date. Dr. Kasten commented on the availability of data from the Cancer Genetics Network, which is managed by NCI but available to all requesters. Although ownership rights have been transferred to NCI, anyone may access the data through a peer-review process. With regard to the quality assurance model, Dr. Jones said the coordinating center should ensure comparability among measures and thus validate data.

Breakout Sessions

Group 1: New Scientific Hypotheses for Cancer Cohorts

Moderator: Joseph Wiemels, Ph.D.

Four presentations were given in this breakout session:

- Copy Number Variation and Childhood Cancer, *Stefan White, Molecular Development Research Group, MCRI, Australia*
- I4C Epigenetics: Global and Gene-Specific Methylation, and Links to Nutritional Factors, *Nicholas Wong, Ph.D., Epigenetics Research Group, MCRI, Australia*
- Epimutation and Disease, and Cord Blood Banking on a National Scale, *David Martin, M.D., Children's Hospital Oakland Research Institute, USA*
- Translocation Screening in a Centralized Laboratory, Scaling Up for a Large Cohort, *Julie M. Gastier-Foster, Ph.D., Director, Cytogenetics/Molecular Genetics Laboratory, Center for Childhood Cancer, Columbus Children's Hospital, USA.*

Group 2: Core Study Protocol and Data Dictionary for Future Analyses

Moderator: Richard Kwok, Ph.D.

Four presentations were given in this breakout session:

- Discussion of the Membership Guidelines, *Carol Kasten, M.D., Geneticist and Medical Officer, Epidemiology and Genetics Research Program, NCI, NIH, DHHS, USA*
- Participating in a Consortium: Experiences from a Cohort, *Jean Golding, Ph.D., D.Sc., Avon Longitudinal Study of Parents and Children, Professor, Department of Community Based Medicine, University of Bristol, UK*
- Participating in a Consortium: International Perspective, *Danuta Krotoski, Ph.D., Acting Associate Director, Prevention Research and International Programs, NICHD, NIH, USA*
- Data Compilation, Next Steps for Future Analyses, *Richard Kwok, Ph.D., Epidemiologist, Environmental Epidemiology and Statistics Program, RTI International, USA.*

Reports from Breakout Sessions

Group 1, Part 1. Dr. Wong summarized the first two presentations for Group 1: New Scientific

Hypotheses for Cancer Cohorts.

The first presentation by Dr. White introduced hypotheses surrounding copy number variation (CNV) and pediatric leukemia. CNV is a type of structural genomic variation that involves the deletion of duplication of regions that are greater than 1 kilobases in length. Specific regions with CNV have been found in many diseases including cancer and have led to a number of questions that could be addressed in a cohort study with respect to pediatric leukemia. The main question posed was to ask if any common CNV exists that correlate with susceptibility to leukemia and whether certain environmental exposures modify the prevalence of the CNV and thus the risk of leukemia. To address this hypothesis, only a small amount (in the order of 100-500 nanograms) of DNA from each individual is required for either a global analysis using SNP DNA microarrays or a targeted analysis using a technique known as Multiplex Ligation-dependent Probe Amplification (MLPA) assay. Both assays are feasible for cohort studies. However, a targeted approach using MLPA is an attractive option over using DNA microarrays in terms of cost and ease of adapting the assay in the lab setting and could be used in the short term to quickly test the CNV hypothesis.

Dr. White's presentation raised the following global questions about copy number variations (CNVs):

- Do any CNVs in children with leukemia correlate with an increased susceptibility to developing the disease?
- Is there an increased number of *de novo* CNVs in children with leukemia compared with controls?
  - Do any environmental exposures during pregnancy correlate with increased numbers of *de novo* CNVs in children?
- Do any parental CNVs lead to an increased probability of having a child that will develop leukemia?
  - Do any of these CNVs correlate with specific environmental exposures?
  - Answering these questions will require assaying genomic DNA from the patient and both parents.

It is not known whether CNVs of specific genes are associated with susceptibility to leukemia. The vitamin D pathway and folate pathway are of particular interest for study. A small amount of genomic DNA—several hundred nanograms—is needed to examine these questions.

The second presentation by Dr. Wong introduced hypotheses surrounding a role for epigenetics in pediatric leukemia. It is widely known that a number of environmental factors including pesticide exposure and infection seem to increase the risk of leukemia. DNA methylation, one of a range of epigenetic markers, has been shown to change in rodent models exposed to such factors. Furthermore, folic acid is the source of precursor required for the DNA methylation reaction (S-adenosyl Methionine) and requires additional dietary co-factors (B-group vitamins) for its metabolism. An alteration of dietary intake will inevitably affect the DNA methylation reaction that could in turn, alter the epigenome. Therefore, a study looking into polymorphisms of the folate pathway genes, maternal dietary intake during gestation and childhood development as well as the epigenome with respect to childhood leukemia is appropriate. Such a study would require serum/plasma to measure folate levels and up to 3 micrograms of genomic DNA for a

combined epigenetic (DNA methylation) and folate gene polymorphism analysis.

Another line of research presented by Dr. Wong involved the role of vitamin D and the vitamin D receptor pathway (VDR) on pediatric leukemia. Vitamin D is synthesized in the skin and is dependent on skin melanin levels and sun exposure. Vitamin D activates VDR which then binds to the promoter of genes and regulates their transcription. Aberrant levels of vitamin D and defective VDR could give rise to dysregulation of gene transcription and lead to increased risk of pediatric leukemia. Indeed there is evidence of a relationship between seasonal variation of pregnancy and the incidence of pediatric leukemia suggests a possible causative role for Vitamin D and the VDR pathway. Furthermore, there is preliminary evidence revealing mothers with extremely low vitamin D levels at 28 weeks gestation can give rise to increased VDR gene promoter hypermethylation of the child at birth. This preliminary work demonstrates the feasibility of performing such an analysis that requires maternal blood for vitamin D level determination and newborn blood spots from Guthrie cards for promoter methylation analysis.

Epigenetic changes could be the mediators of environmental exposures and can modulate leukemia risk. The extent of such changes could be influenced by copy number variation of genes pivotal in the folate and vitamin D pathways. Single nucleotide polymorphisms can also have similar effects. Thus investigating these factors should be a top priority for the I4C and questions to address these have been summarized in the report of the breakout sessions.

Dr. Wong's presentation raised the following global questions about epigenetics and DNA methylation:

- How are global DNA methylation levels in newborns related to maternal dietary folate factors with respect to leukemia?
- Is there a relationship between maternal dietary folate, circulating newborn folate levels, and incidence of childhood leukemia?
- Is there a common global DNA methylation signature (genome-wide promoter methylation) associated with the incidence of childhood leukemia?

Dr. Wong posed the following questions about nutrition:

- Do folate/vitamin D levels in children and their parents correlate with leukemia incidence?
- Are folate/vitamin D receptor gene sequence variants associated with an increased risk of leukemia?
- Is folate/vitamin D receptor gene promoter hypermethylation associated with higher incidence of leukemia?
- Is there an interaction between diet and genetic/epigenetic variation of the folate/vitamin D receptor pathway that predisposes to leukemia?

Several micrograms of genomic DNA will be needed to address these questions. Samples of whole blood are also needed to measure folate and vitamin D levels. The evidence for the connection between vitamin D and folate pathways and leukemia was discussed. The vitamin D pathway:

- Has been shown to have a protective effect for leukemia, suggesting the association between defects and increased risk
- Is known to be influenced by the environment

- Has been shown to affect tumor cell proliferation in prostate cancer.

Epidemiological evidence has shown connections between these two pathways and leukemia:
- A study has shown that children born during winter months have a higher incidence of leukemia, suggesting an association between leukemia and maternal sun exposure during gestation.
- Some folate gene pathway polymorphisms have been shown to have a protective effect against leukemia. Past studies have not examined dietary levels of folate.

Group 1, Part 2. Dr. Wiemels summarized the last two presentations from Group 1.

Dr. Martin gave a presentation for Bertram Lubin, M.D., director of the Children's Hospital Oakland Research Institute (CHORI). Dr. Lubin has developed a national cord blood bank, made up of samples from siblings of children with rare genetic diseases. CHORI's standardized procedures for collecting cord blood may be adapted to the Study, which will collect samples on a much larger scale.

Dr. Martin presented his own research on epigenetics. His work focuses on genetic errors that may arise early in stem cell, germ cell, or embryo formation that increase the risk of disease. He hypothesized that epimutations that affected known disease genes could be found because they would cause a disease similar to known inherited cancer syndromes. Dr. Martin studied families who have symptoms of hereditary nonpolyposis colorectal cancer syndrome but do not have a DNA-based mutation for the disease. He found that these individuals had a germ-line epimutation in their MLH1 gene. It is not known which genes could be used to test this hypothesis for childhood cancer.

Dr. Gastier-Foster presented new technologies for screening for genetic defects in childhood leukemia samples. It is easier to find translocations in a leukemia sample than to find a rare translocation in a sample taken at birth. The participants discussed testing for rare translocations at multiple laboratories and then comparing results. A subcommittee is needed to develop protocols for translocation testing.

Although translocations are the most accessible hypothesis, testing is difficult because it requires RNA-based assays (studying epigenetics and CNVs only requires DNA-based assays). New technologies allow screening for multiple translocations at once. Translocation screening could be conducted in two stages. The first stage would identify positive samples, and the second stage would validate the results to eliminate false positives. This would require the storage of multiple aliquots. The sample size, costs, and methods for translocation screening were discussed:
- Ideally, all patients would be screened to identify a large cohort with translocations for continued study.
- If a smaller sample size is used, it would be more difficult to show that translocation frequencies are comparable between cohorts and studies.
- Perfect cord blood samples—samples suitable for transplantation—could be collected from all patients, but this may be costly. Dr. Wiemels will follow up with Dr. Lubin about the cost of this type of sampling.
- There are simpler, cheaper sampling methods, but these may not preserve cells adequately.

- Protocols may need to be developed that balance cost and quality. If RNA stabilizing agents do not interfere with assays, their use may simplify sampling.
- Existing cohorts have not created a cord blood bank suitable for the translocation assay.
- Screening must be able to detect rare translocations, occurring with a frequency of 1/100 or 1/1,000.
- The samples collected for the translocation assay may be useful for other studies.
- Subcommittees need to develop specific, promising hypotheses to provide a rationale for sample collection. These hypotheses may be global or focus on high-risk subgroups.

Group 2. Dr. Kwok summarized the breakout session for Group 2: Core Study Protocol and Data Dictionary for Future Analyses.

The session participants discussed membership guidelines:
- There are three categories of membership: those affiliated with a contributing cohort, sponsors of a cohort or the I4C, and other scientific experts.
- Each cohort should be given the opportunity to choose to participate in the study of a particular hypothesis. Participation in all I4C activities should not be assumed.
- The advisory committee should be eliminated. Its work is redundant with some of the subcommittee work.

Project participation and authorship should:
- Allow opportunities for participation in publications when an analysis is proposed
- Require communication to membership at-large to participate within a certain time window when a new analysis is proposed
- Have a formal process for the I4C Steering Committee to adjudicate disputes about authorship.

It was proposed that all I4C papers be authored under the I4C group heading, with a subsection listing individual authors. From the perspective of cohorts:
- A central coordinating center is necessary to ensure the validity and reliability of sample collection and analysis.
- Best practices guidelines would be useful for standardization. These should be detailed in policies and procedures guidelines.

From an international perspective, the following issues should be considered:
- Sensitivity to language and cultural differences (such as back translation), especially during data collection efforts
- Institutional review board (IRB) and ethical considerations
  - New models to streamline IRB relationships
  - Potential to have a dedicated I4C IRB
- Need for a central coordinating center to coordinate efforts
- Issues of intellectual property rights and the transport of data and specimens.

The next steps are to:
- Revise membership guidelines and the policy and procedures manual to reflect the discussions at this meeting

- Pursue I4C hypotheses of interest
  - Forming hypothesis-specific subcommittee
  - Assessing validity of the relevant hypotheses variables of interest
  - Providing data dictionaries
- Start analyses.

The formation of an administrative policy subcommittee was proposed.

Potential IRB and ethical issues with using de-identified data were discussed. Committees around the world have different definitions of informed consent. For some, generic consent is not informed consent. Patients must be informed of specific studies and procedures. In another pooled data study, patients are dropped if there is any question of consent. The purpose of pooled studies is to look at the big picture. The meaning of informed consent for childhood studies may need further clarification.

Several participants commented on the need for a coordinating center. Issues discussed included:
- Whether a coordinating center should be attached to the I4C or whether the I4C should have its own core group
- What kind of coordination is needed
- Whether IARC or NCI could provide support to help coordinate the consortium.

This discussion was tabled for a future meeting.

Strategies for Funding

Danuta Krotoski, Ph.D., Acting Associate Director, Prevention Research and International Programs, NICHD, NIH, DHHS, USA

Dr. Krotoski reviewed strategies for funding large longitudinal studies such as I4C. Activities such as administration/coordination, pilot studies, and support for common projects require financial support. Support for common projects includes individual cohort supplements for data acquisition, consortium support for data management and analysis, training, repositories (if any), and publication and communication costs. Administration and coordination are required to support the Steering Committee activities, organize meetings of consortium members, and implement consortium guidelines including those related to ethical issues and intellectual property. Administration and coordination funding is needed for conference grants to support annual consortium meetings and sponsorship for overarching administrative support from major funding sources.

Pilot studies are needed to test individual hypotheses. Funding for pilot studies is available from NIH through R21 and R03 grants up to $175,000 per year for 2–3 years. In addition, collaborative funding may be possible among the EU, NIH, and private partnerships. Small grants such as fellowship grants from private foundations may be available for training new investigators.

Support for common hypotheses and data acquisition will be needed. No one funding source will be sufficient to support the I4C projects. Partnership among funding institutions will be critical.

I4C members should develop multinational cooperative agreements for 2009 funding cycles that will include funds for administration and individual cohort activities. Individual cohorts should seek supplemental funding from national funding bodies.

There are three initial steps for I4C funding: (1) assess actual financial and administrative needs for the consortium as currently composed, (2) develop a timeline for individual hypotheses, and (3) analyze data collection, analyses costs, and consortium participants.

Potential funding partners include:

- National and regional research funding bodies such as NCI, NIH, EU, EPA, and CDC
- Multilateral organizations such the WHO, its regional offices, and the United Nations Environment Program
- Private foundations that focus on prevention of childhood cancers such as Action for International Cancer Research, Children's Cancer Foundation, American Cancer Society, and Cancer Research UK.

Dr. Krotoski proposed next steps for funding: (1) involve funding partners in I4C plans and activities, (2) communicate the value of consortium research to establish political will to fund this multinational approach, and (3) develop collaborative research proposals.

Research Support Mechanisms

Carol Kasten, M.D., Geneticist and Medical Officer, Epidemiology and Genetics Research Program, NCI, NIH, DHHS, USA

Dr. Kasten briefly reviewed DCCPS research support activities. The DCCPS supports a broad range of studies, including gene discovery, gene penetrance, effect modification (gene-gene, gene-environment interactions), analytical methods for genetic epidemiology and risk assessment, behavioral and clinical research on genetically susceptible populations (observational and interventions), case-control studies, cohorts, and consortia.

Dr. Kasten characterized some DCCPS research support mechanisms. R-series grants are used when (1) an investigator is free to carry out her/his research without frequent NIH involvement; (2) NCI does not expect to receive a product for use by NCI; (3) various program announcements are published in the NIH Guide; and (4) the research is investigator-initiated. R03s are small research grants for studies of extant data. They have a short project period of 2 years and total direct costs of $50,000 per year. R03s may not be used for thesis or dissertation research. R13 conference grants support regional, national, or international meetings, conferences, or workshops. The grant applicant must be a U.S. citizen. R21 grants support exploratory and developmental projects in fields of biomedical, behavioral, or clinical research. They provide support for early/conceptual stages of research. Topics should have the potential to enhance health-related research (for example, feasibility of a novel area of investigation; a new experimental system; or development of novel techniques, agents, methodologies, models or applications). K series grants support individual education/training—primarily for doctoral or medical degrees or both depending on the grant. K series grants are available only to U.S. citizens or foreign citizens who are permanent residents in the United States.

Discussion. Dr. Golding clarified that R-series grants are available to non-U.S. citizens provided they can show that their research cannot be done in the United States. R-series grants have funded special studies in Nordic countries that have used linked registries. R-series grants may be an ideal funding mechanism for certain I4C studies. Dr. Dwyer suggested that I4C collaborators consider one funding request to one funding institution for a single grant to address a specific scientific question. From the initial grant request would follow other requests to continue or expand the research. For example, R01 funding from NIH would encourage funding from comparable agencies in other countries. Dr. Kasten noted that U24 grants are available to support research infrastructure. Dr. Scheidt said the I4C needs to begin analyzing data for its proof-of-concept hypotheses. There are two options: (1) one of the participating institutions needs to fund an I4C investigator or (2) one of the I4C investigators needs to apply for funding. An R03 grant could be used to begin data analysis, but—according to Dr. Kwok—there is no data set currently ready for analysis. A subcommittee could establish priorities for data set analyses. An R03 grant could fund an initial proof-of-concept study. Additional funding could support regular I4C meetings.

Establishment of Committees and Subcommittees

Martha S. Linet, M.D., M.P.H., Chief, Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, NCI, NIH, DHHS, USA
Peter C. Scheidt, M.D., M.P.H., Director, National Children's Study, NICHD, NIH, USA

According to Drs. Linet and Scheidt, there is a need for several new committees:

1) Hypothesis-Specific Subcommittees will be formed, with the Steering Committee assuming responsibility for identifying potential hypotheses and determining the priorities for hypothesis testing. Hypotheses can be proposed by anyone in the I4C, and can be based on existing data, or the subcommittee may determine the need for a feasibility pilot study for some of the genetic and molecular aspects. Proposed members of the specific hypothesis subcommittees are as follows:
   - Birth Weight Hypothesis Subcommittee
     - Terry Dwyer, M.D., M.P.H.
     - Jean Golding, Ph.D., D.Sc.
     - Andrej Grjibovski, M.D.
     - Carol Kasten, M.D.
     - Richard Kwok, Ph.D.
     - Nancy Potischman, Ph.D.
     - Sharon Savage, M.D.
     - Joachim Schüz, Ph.D.
   - Infection Hypothesis Subcommittee
     - Jean Golding, Ph.D., D.Sc.
     - Eve Roman, Ph.D.
   - Translocations Hypothesis Subcommittee
     - Jacqueline Clavel, Ph.D.
     - Julie M. Gastier-Foster, Ph.D.
     - Kjeld Schmiegelow, M.D., Dr.Med.Sci.
     - Stefan White, Ph.D.
     - Joe Wiemels, Ph.D.

  - Nick Wong, Ph.D.
- Paternal Age Hypothesis Subcommittee
  - Silvia Brandalise, M.D.
  - Terry Dwyer, M.D., M.P.H.
  - Jean Golding, Ph.D., D.Sc.
  - Andrej Grjibovski, M.D., Ph.D.
  - Richard Kwok, Ph.D.
  - Jørn Olsen, M.D., Ph.D.
- Folate Hypothesis Subcommittee
  - Robert J. Berry, M.D.
  - Jacqueline Clavel, Ph.D.
  - Terry Dwyer, M.D., M.P.H.
  - Jean Golding, Ph.D., D.Sc.
  - Rayjean J. Hung, Ph.D.
  - Richard W. Jones, D.Phil., Ch.B., M.B.
  - Richard Kwok, Ph.D.
  - Martha Linet, M.D., MPH
  - David Martin, M.D.
  - Sjurdur F. Olsen, Ph.D.
  - Nancy Potischman, M.D.
  - Joe Wiemels, Ph.D.
  - Stefan White, Ph.D.
  - Nicholas Wong, Ph.D.
  - Li Zhu, M.D., M.P.H. (or group representative)
- Pesticides Hypothesis Subcommittee
  - Silvia Brandalise, M.D.
  - Rebecca C. Brown, M.P.H., M.E.M.
  - Joachim Schüz, Ph.D.

2) Outcomes Review Committee will focus on the requirements for outcome assessment including the requirements for histopathologic and molecular diagnostic review. Proposed members are:
   - Silvia Brandalise, M.D.
   - Richard Kwok, Ph.D.
   - Martha S. Linet, M.D., M.P.H.
   - Sharon Savage, M.D.

3) Biospecimens Committee would begin to address the types of biospecimens/samples to collect and, with epidemiologists, identify field-ready approaches. Proposed members are:
   - Julie M. Gastier-Foster, Ph.D.
   - Richard W. Jones, D.Phil., Ch.B., M.B.
   - David Martin, M.D.
   - Mads Melbye
   - Sharon Savage, M.D.
   - Kjeld Schmiegelow
   - Stefan White, Ph.D.

- Joe Wiemels, Ph.D.
- Nick Wong, Ph.D.
- Li Zhu, M.D., M.P.H. (or group representative)
- NCS expert (TBA).

4) Policies and Procedures Committee. Proposed members are:
   - Rebecca C. Brown, M.P.H., M.E.M.
   - Richard Kwok, Ph.D.
   - Martha S. Linet, M.D.
   - Jørn Olsen, M.D., Ph.D.
   - Peter C. Scheidt, M.D., M.P.H.

5) Ethics and Bioethics/IRB/Consent Committee. Proposed members are:
   - Silvia Brandalise, M.D.
   - Karen Birmingham
   - Carol Kasten, M.D.
   - Danuta M. Krotoski, Ph.D.

Wrap-Up of Meeting and Next Steps

Terry Dwyer, M.D., M.P.H.

The following locations were nominated for upcoming I4C meetings:

- Melbourne, Australia
- Geneva, Switzerland (Brocher Foundation facilities)
- Latin America
- Lyon, France (IARC facilities).

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