

# Challenges in Pediatric Inflammatory Bowel Disease

*Athos Bousvaros, MD, MPH, Francisco Sylvester, MD, Subra Kugathasan, MD, Eva Szigethy, MD, PhD, Claudio Fiocchi, MD, Richard Colletti, MD, Anthony Otley, MD, Devendra Amre, MD, George Ferry, MD, Steven J. Czinn, MD, Judy B. Splawski, MD, Maria Oliva-Hemker, MD, Jeffrey S. Hyams, MD, William A. Faubion, MD, Barbara S. Kirschner, MD, Marla C. Dubinsky, MD, and the Members of the Challenges in Pediatric IBD Study Groups*

**Abstract:** It is estimated that of the >1 million individuals in the United States with inflammatory bowel disease (IBD), ≈100,000 are children. IBD that begins in childhood affects the individual at a critical period of growth and development. Children with Crohn's disease and ulcerative colitis may experience complications such as growth failure, school absence, and depression. In addition, because children with IBD have fewer environmental confounders such as smoking, children may be an excellent population to study microbial and immune interactions. Despite these opportunities, the discipline of pediatric IBD investigation is still in its infancy.

In September of 2005, a group of investigators with expertise in pediatric IBD met in Boston (Massachusetts) to review the current status of childhood IBD research and to develop research priorities that warranted funding from the Crohn's and Colitis Foundation of America. The group included pediatricians, internists, basic scientists, clinical investigators, and members of the administrative staff and board of the Crohn's and Colitis Foundation of America. The research needs in respective areas were outlined by the heads of 10 focus groups, each with expertise in their respective fields (genetics, psychosocial issues, epidemiology, microbiology, immunology, quality improvement, pharmacogenomics, nutrition, growth and skeletal health, and clinical trials). Before the conference, heads of the research focus groups developed their proposals with experts in the field. At the end of the conference, members of the focus groups and members of the steering committee rated the proposed areas of study in terms of feasibility and importance. It was recommended that the Crohn's and Colitis Foundation of America focus its initial efforts in pediatric IBD in 5 areas: the effects of inflammation on growth and skeletal development, the genetics of early-onset IBD, the development of quality improvement interventions to standardize and improve clinical care of children with IBD, the immunology of childhood IBD, and the

diagnosis and treatment of psychosocial sequelae of childhood IBD. At the conclusion of the meeting, investigators discussed the formation of a multicenter collaborative network to advance clinical and basic research in the field.

**Key Words:** inflammatory bowel disease, Crohn's disease, ulcerative colitis, pediatric, child, genetics, immunology, quality improvement, growth, bone, osteopenia, nutrition, psychosocial, depression, anxiety, epidemiology, microbiology, pharmacology, pharmacogenomics, clinical trials

(*Inflamm Bowel Dis* 2006;12:885-913)

## I. EXECUTIVE SUMMARY

### Crohn's and Colitis Foundation of America Research Priorities

Inflammatory bowel disease (IBD) is an umbrella term for a group of diseases, of which Crohn's disease and ulcerative colitis are the 2 main types. IBD is ranked among the 5 most prevalent gastrointestinal diseases in the United States, with associated healthcare costs exceeding \$1.7 billion annually. Estimates indicate that as of 2005, ≈1.4 million Americans have been diagnosed with IBD. Roughly 10% of them are children and adolescents under the age of 17.

Although the study of pediatric IBD may yield important information applicable to the disease in both children and adults, most of the scientific information about and therapeutic approaches for IBD have been obtained by studying adult patients, animal models, and cells in culture. Consequently, there is an urgent need for research in pediatric IBD.

Recognizing this need, the Crohn's and Colitis Foundation of America (CCFA) launched an initiative known as Challenges in Pediatric IBD. It began with the formation of 10 focus groups composed of specialists in various disciplines who were commissioned to survey the current state of knowledge in pediatric IBD and to identify pressing issues that need to be addressed. From those discussions, each group prepared a position paper describing its findings and recommending research projects that would enhance our

Received for publication May 5, 2006; accepted May 12, 2006.

A full list of titles and academic affiliations is listed in the Appendix.

Reprints: Athos Bousvaros, MD, MPH, Children's Hospital Boston, Inflammatory Bowel Disease Center, Hunnewell Bldg, First Floor, 300 Longwood Ave, Boston, MA 02115 (e-mail: athos.bousvaros@childrens.harvard.edu)

Reprints: Marjorie Merrick, Director of Research and Education, Crohn's and Colitis Foundation of America, 386 Park Ave S, Floor 17, New York, NY 10016-8804.

Copyright © 2006 by Lippincott Williams & Wilkins

understanding of pediatric IBD and lead to improved treatment strategies.

The focus groups were in the following areas: genetics, psychosocial issues, epidemiology, microbiology, immunology, quality improvement and safety, pharmacogenomics, nutrition and diet, growth and skeletal health, and clinical trials. To carry this initiative forward, CCFA then organized a conference in Boston on September 23–25, 2005. The meeting brought together clinical and basic science researchers who heard presentations from representatives of the 10 focus groups and discussed their recommendations for research. This white paper summarizes the proceedings of that meeting.

At the conference, it was recognized that one of the advantages of studying pediatric IBD is that the onset of disease occurs at a young age, when there are fewer environmental confounders that complicate research, compared with IBD in adults. In addition, there is strong commitment on the part of the patients' parents, as well as investigators and clinicians, to improve the quality of life (QOL) of children with IBD. CCFA, the National Institutes of Health (NIH), the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN), and other organizations are highly committed to sponsoring basic, translational, and clinical research in pediatric IBD.

On the other hand, one of the limitations of studying pediatric IBD is that a relatively small number of patients are available for study at any particular institution. In addition, the number of investigators in pediatric IBD is relatively small. Thus, such research requires ongoing collaborations between many investigators and institutions. It was suggested that a pediatric component be included in all studies of IBD sponsored by CCFA.

The conference participants considered the importance of each proposed research item and its feasibility in terms of manpower and resources available. On the basis of their discussions, they assigned the highest priorities to the following 5 areas, each with specific aims:

### **Growth and Skeletal Health**

- a) To understand the availability and utilization of nutrients necessary to achieve normal growth, body composition, and progression through puberty.
- b) To better understand key endocrine abnormalities in children with IBD and to identify the significant determinants of those most at risk.
- c) To study the efficacy of modalities used to treat IBD in children on growth and body composition, including pharmacological and nutritional therapies.
- d) To define changes in bone modeling and remodeling associated with the inflammatory response in IBD in children.
- e) To test the best interventions to optimize bone mass in children with IBD so that they can reach their genetically determined peak bone mass.

- f) To understand the natural history of bone mass accrual and bone structure in children and adolescents with IBD and to differentiate between decreased bone accrual and increased bone loss.

### **Genetics**

- a) To identify the susceptibility and modifier alleles associated with early age of onset (before 12 years of age) of Crohn's disease and ulcerative colitis using the whole-genome association approach.
- b) To perform genotype-phenotype correlation studies and gene-environment interaction studies of prospectively identified, well-characterized IBD patients in a large, exclusively pediatric-onset IBD cohort.

### **Quality Improvement**

- a) To identify underuse, overuse, and misuse of diagnostic and therapeutic interventions and to identify gaps between recommended and actual care so that the gaps can be closed.
- b) To form an Improvement Collaborative to improve the detection, treatment, and prevention of growth delay and growth failure in children with Crohn's disease and ulcerative colitis.

### **Immunology**

To study changes from early-onset to late-phase pediatric IBD in the following areas: innate and adaptive immunity, developmental aspects of mucosal immunity, target antigens of the immune response, and effects of therapy on the immune response and immune function.

### **Psychosocial Issues and Development**

- a) To identify risk and protective factors regarding depression, anxiety, and related psychosocial difficulties in both children and adolescents with IBD. These studies could include a focus on both biological and social factors to better understand the interactions that involve the brain, gut, immune system, and environmental influences.
- b) To conduct randomized treatment and prevention studies aimed ultimately at reducing emotional suffering (particularly anxiety and depression) and at improving global functioning. There is a particular need for specific focus on areas such as medical outcome, medical adherence, social competence, and quality-of-life issues.

In addition to identifying these priorities, the conference participants recognized the need to set up a pediatric IBD collaborative network that would serve as a resource for studies by scientists and clinicians in the field. The network would include several sections, each devoted to supporting separate groups of studies such as translational research, clinical trials, and quality improvement efforts. In addition to these separate research sections, a central governing body would be needed to coordinate and facilitate research efforts.

These types of studies are expected to lead to better care for children and adolescents with IBD, resulting in significant decreases in morbidity, improvement in QOL, and eventually methods of preventing and curing IBD.

## II. PEDIATRIC IBD: A BRIEF INTRODUCTION

Crohn's disease and ulcerative colitis are chronic, debilitating conditions that affect the gastrointestinal tract. They are distinctly different illnesses but are grouped together as IBD because they produce similar signs and symptoms, including intestinal inflammation, abdominal pain, and diarrhea. Crohn's disease can affect any portion of the gastrointestinal tract, whereas ulcerative colitis is restricted to the colon. The exact factors that trigger these diseases are still unclear, but research indicates that these illnesses occur in genetically susceptible individuals whose immune systems react abnormally to environmental agents (such as infectious agents) in the intestines.

Recent studies suggest that the prevalence of IBD is rising in both developed and developing countries. In addition, preliminary data suggest an increase in the incidence of pediatric IBD, including a rise in incidence among children in certain minority communities.

Researchers and clinicians generally agree that pediatric IBD has many characteristics that distinguish it from adult-onset IBD. For instance, the *NOD2/CARD15* gene (on chromosome 16) and the *IBD5* locus (on chromosome 5) are associated with susceptibility to Crohn's disease in adults, but this association is less clear in childhood IBD. Perhaps other genetic loci influence the onset of pediatric IBD. In addition, boys younger than 16 years of age appear to be at higher risk for Crohn's disease than females, but the risk for females increases in older age groups.

In the youngest children with IBD (under 2 years of age), a large subgroup has indeterminate colitis, whereas ulcerative colitis predominates in children between the ages of 3 and 5 and Crohn's disease affects the majority of those older than 6 years of age. This type of pattern, not observed with adult IBD, emphasizes the importance of studying genetic and age-related immunological differences in pediatric IBD.

Evidence from animal models of IBD and preliminary observations in children support the concept that IBD develops in distinct phases and that key mediators of inflammation play different roles, depending on the stage of the disease. These results underscore the importance of taking into consideration the time course of disease when studying pediatric IBD and targeting appropriate treatments.

One clear challenge for children with IBD, especially Crohn's disease, is that their growth and skeletal development are often impaired. An important reason for this problem is lack of adequate nutrition, which in turn can result from decreased caloric intake, increased needs, increased enteral

losses, and altered nutrient utilization. In addition, cytokines and other factors related to the immune system can influence growth directly and indirectly by affecting key hormonal axes. Consequently, both skeletal and sexual maturation may be delayed. Appropriate anti-inflammatory therapy and nutrition can help overcome growth failure and restore pubertal progression, but these measures are not always successful. As a result, some children with IBD do not reach their predicted preillness height potential.

Moreover, children and adolescents with IBD have relatively high rates of depression and anxiety, in part because of the waxing and waning course of this chronic illness. Psychosocial difficulties may take the form of family conflict, trouble socializing with peers, medical adherence problems, and absences from school and extracurricular activities. Taken together, these problems can decrease the QOL for the affected children.

Pathogenic events leading to pediatric IBD may occur any time from shortly after birth until the late teens, but it is difficult to determine when intestinal inflammation actually begins. Nonetheless, studying IBD in pediatric cases has several advantages. These are based on the relative lack of confounders such as comorbidities, complications, previous surgeries, and concomitant medications in children compared with adults. Thus, children with IBD provide the opportunity to investigate such areas as (1) the natural history of the disease, (2) the impact of early environmental influences on disease development, (3) associations between genotype and phenotype, (4) the initial host immune response, and (5) the effects of early interventions with therapeutic drugs. Research with pediatric populations is especially likely to yield helpful information on the triggers and pathogenic mechanisms of IBD in children and adults.

## III. BACKGROUND

The CCFA organized the Challenges in Pediatric IBD conference to bring together clinical and basic science investigators in various disciplines. This meeting was aimed at setting a research agenda that would prioritize the most pressing issues in pediatric IBD.

This conference marked a new and important step in CCFA's ongoing efforts to promote research in IBD. A report of the original initiative, Challenges in Inflammatory Bowel Disease Research Agenda, was released in 1990. It compiled, for the first time, the state of investigations into the pathogenesis and treatment of IBD. That was followed by reviews and updates in 1993, 1998, and 2002. These initiatives focused on adult-onset IBD.

The early Challenges meetings looked at 2 research categories separately: (1) basic science research, involving investigations into the physiology, pathophysiology, and mechanisms of IBD, and (2) clinical science research, dealing

with therapeutic approaches for patient care. As technologies developed, they narrowed the time lag between discoveries in basic science and their clinical applications, blurring the lines between basic and clinical research. Consequently, the 2002 meeting dealt with both areas of research.

The 2005 conference, by extension, was designed to include perspectives on basic, translational, and clinical research in pediatric IBD. This document summarizes the research areas discussed at that meeting, including some background information about the area, deficiencies in our current knowledge, recommendations for research, and the feasibility of each proposed research project. The finalized research agenda is presented in a separate section.

#### IV. STEPS TOWARD ESTABLISHING THE RESEARCH AGENDA

Following the earlier pattern of Challenges in IBD Research initiatives, CCFA adopted a 3-phase approach designed by Stephan Targan, MD. The entire process, involving months of efforts, was guided by a steering committee consisting of 11 leading scientists and clinicians with specializations and interests in adult and pediatric IBD. The steering committee was chaired by Athos Bousvaros, MD, MPH.

During phase 1, specialists from a broad range of disciplines formed 10 focus groups, with 5 to 8 members per group. The groups were in the following areas: (1) genetics, (2) psychosocial issues, (3) epidemiology, (4) microbiology, (5) immunology, (6) quality improvement and safety, (7) pharmacogenomics, (8) nutrition and diet, (9) growth and skeletal health, and (10) clinical trials. These groups held independent discussions on the current state of knowledge and the pressing issues that need to be addressed in pediatric IBD from the standpoint of their respective disciplines. From those discussions, each group prepared a position paper describing its findings and proposing a prioritized list of research projects or "research actions" that would enhance our understanding of pediatric IBD and lead to improved treatment strategies.

Phase 2 consisted of a 3-day conference in Boston sponsored and organized by CCFA, with additional input provided by the leadership of NASPGHAN. It brought together members of the steering committee, the chairpersons or representatives of each focus group, special guest advisors, and representatives of CCFA. Before the meeting, each participant received a set of position papers generated by the focus groups. Dr Bousvaros and 2 other members of the steering committee, Barbara Kirschner, MD, and Marla Dubinsky, MD, moderated the proceedings.

During the conference, the chair or representative of each focus group presented an overview of the findings of that group, culminating with a short list of high-priority actions proposed by the group. Each presentation was discussed at length, and the proposed research projects were examined on

the basis of their importance for pediatric IBD, their feasibility, and the technologies and other resources needed to carry them out. Once all the reports were heard and discussed, the steering committee members and focus group representatives examined the research action items together, voted on them, and selected 5 project areas that were to receive the highest priority.

Phase 3 involved development of this white paper, which presents the issues addressed and items prioritized during phases 1 and 2. The full text of the position papers of the 10 focus groups may be viewed on-line at [www.ccfaprofessionals.org](http://www.ccfaprofessionals.org).

#### V. SUMMARIES OF ISSUES ADDRESSED BY FOCUS GROUPS

Representatives of the 10 focus groups presented and discussed a wide range of issues in pediatric IBD based on their respective scientific disciplines and areas of interest. Summaries of these issues are given below.

##### 1. Genetics

Presentation by Subra Kugathasan, MD.

##### 1.1. Background

Several lines of evidence suggest that there is significant genetic contribution to susceptibility to IBD: (1) There is a high degree of concordance among monozygotic twins; (2) there is increased susceptibility to IBD among first- or second-degree relatives of affected individuals; (3) whole-genome linkage scans have revealed linkage between IBD and several genomic regions; and (4) several mutations/single-nucleotide polymorphisms (SNPs) have been found to be associated with increased susceptibility to IBD.

Alleles of the *NOD2/CARD15* gene have been found to constitute a reliable, reproducible risk factor for the development of Crohn's disease. In addition, multiple cohort studies have confirmed the association of the IBD5 locus with Crohn's disease in adults. Although initial studies suggested that the association of *CARD15* with susceptibility to Crohn's disease was higher for pediatric-onset disease, recent work with children suggests that this association in pediatric cases is roughly comparable to adult-onset disease. Furthermore, the association between the IBD5 locus and the risk of Crohn's disease is weaker for children than for adults. It appears, therefore, that there may be early-onset (pediatric-onset) genes waiting to be discovered.

##### 1.2. Deficiencies in Current Knowledge

So far, very little effort has been dedicated toward identifying susceptibility genes in exclusively pediatric-onset IBD. Consequently, our genetic knowledge in pediatric IBD is rudimentary. This deficiency of knowledge underscores the importance of finding susceptibility genes for early-onset disease and delineating pathophysiological mechanisms that distinguish pediatric-onset from adult-onset IBD.

### 1.3. The Case for Studying Pediatric IBD Genetics

Various arguments have been advanced to support the hypothesis that the genetic contribution is greater for pediatric-onset IBD than for adult-onset IBD. Children at a younger age of IBD onset are more likely to have a family history of IBD than those at an older age of onset. Compared with adult onset, childhood onset may have greater gene mutation dosage (hence earlier presentation). Finally, childhood-onset IBD is more likely to be based on genetics, with very little time for environmental modifiers such as smoking to act.

Several inception cohorts are available for prospective follow-up of children with IBD. These cohorts are not subject to “recall bias” in data collection or phenotyping. Moreover, parents and siblings of affected individuals are readily available for DNA collection. Also, because pediatric cohorts have less time for environmental exposures (including smoking), it is possible to reduce or eliminate major confounding variables.

### 1.4. Recommendations for Research

#### (1a) Susceptibility alleles

Identify the susceptibility alleles associated with early-onset Crohn’s disease and ulcerative colitis. This can be done by several approaches, including the whole-genome association approach or a genome-wide scan to identify peak limit of detection scores in pediatric-onset cohorts. The whole-genome association approach is a high-throughput genotyping technology involving the use of gene chips that allow the simultaneous screening of  $\geq 500,000$  SNPs. These SNPs have been selected intelligently by obtaining data from the International HapMap Project.

#### (1b) Genotype-phenotype-serotype correlation studies

Perform genotype-phenotype-serotype correlation studies in well-characterized IBD patients in a large, exclusively pediatric-onset prospective cohort. For this research goal, it will be important to have accurate, standardized phenotyping tools. The phenotyping tools currently used by the International IBD Genetics Consortium and the NIH Genetics Consortium need to be refined to reduce intercenter variations in classification and to include pediatric needs such as growth and pubertal issues.

#### (2) Collaborative network

A North American pediatric IBD collaborative network needs to be established or modified from existing inception cohorts, with a component dedicated to pediatric IBD genetics.

### 1.5. Potential Obstacles

- Accurate, standardized phenotyping tools specific to children need to be developed.

- Misclassification bias during diagnosis of the disease is more common in pediatrics.
- Appropriate, age-matched controls are needed.
- Distribution of academic credits among investigators in a network needs to be worked out.
- Ethical issues relating to patient confidentiality, genetic research, and DNA storage need to be clarified with medical ethicists and local Institutional Review Boards.
- One concern is whether there will be enough samples available for replication of the results.
- Adequate funding is needed.

### 1.6. Proposed Action Items

1. Identify susceptibility and modifier alleles for early-onset (before age 12) Crohn’s disease and ulcerative colitis using the whole-genome association approach.
2. Perform genotype-phenotype correlation studies and gene-environment interaction studies in prospectively identified, well-characterized IBD patients using a large, exclusively pediatric IBD cohort.

### 1.7. Issues Discussed

It was recognized that the term “early-onset IBD” needs to be clearly defined. First, the cutoff age needs to be agreed on. One suggestion was to choose age 12 as the cutoff age, so that “early-onset IBD” would refer to the prepubertal age group. Second, it is difficult to pinpoint the age of onset of IBD until after symptoms have appeared and a diagnosis is made. Dr Kugathasan’s group has chosen to link the age of onset to the date on which the pediatric patient first has a procedure that leads to a diagnosis of IBD.

The difficulty of obtaining a sufficient number of children for a study was discussed. The suggested approach was to form a network and work collaboratively with other investigators and established consortia.

It was agreed that when DNA samples are being collected, it would be worth saving some serum samples and biopsies for future studies in proteomics that may shed light on proteins associated with the IBD-related genes.

Environmental modifiers or triggers of IBD need to be studied in association with the genetic factors. A study of gene-environment interactions would need about 2000 to 3000 subjects with the appropriate controls.

It was noted that in addition to studying the genetics of patients at the time of inception of IBD, it would be important to perform similar studies of established patients with the same age of onset. Disease progression and its complications would be better understood by examining the latter group of patients.

CCFA is maintaining and expanding its own cell line bank. This resource is available to researchers around the world for their studies.

## 2. Psychosocial Issues and Development

Presentation by Eva Szigethy, MD, PhD.

This focus group identified several areas related to psychosocial problems facing children and adolescents with IBD: (1) psychopathology, (2) health-related QOL (HRQOL), (3) psychosocial functioning, (4) medical adherence, (5) neuropsychiatric aspects of IBD, and (6) treatment/prevention of psychiatric/psychosocial dysfunction.

### 2.1. Psychopathology

#### 2.1.1. Background

The majority of studies report increased rates of depression and anxiety in children and adolescents with IBD compared to healthy control subjects, siblings, and youth with other chronic physical illnesses. Risk factors associated with increased depressive severity include clinical disease activity, older age, family conflict, parental depression, and poor social support.

#### 2.1.2. Deficiencies in current knowledge

- Many prior studies were based on small sample sizes, heterogeneous definitions of psychopathology, and self-report questionnaires instead of clinician-rated psychiatric interviews. Additionally, standardized scores frequently were not reported, making it difficult to assess clinical significance of the findings.
- We need a better epidemiological determination of the prevalence of depression and anxiety, along with their severity measured with validated instruments.
- We need to determine the prevalence of comorbid irritable bowel syndrome and/or functional abdominal pain.
- The role of denial as a maladaptive coping strategy has not been adequately addressed in the pediatric IBD population.
- The manifestation of psychopathology in prepubertal children with IBD has not been adequately compared with that in adolescents with IBD.

#### 2.1.3. Recommendation for research

- Aim: Conduct a more comprehensive assessment of prevalence of psychiatric diagnoses and risk factors that predict anxiety and depression using validated instruments in larger cohorts of youth with IBD.
- Logistical support: Achieving this aim will need evaluators with appropriate training in psychiatric interviewing and multisite studies.
- Obstacles: Thorough interviews of parent and child may take 1 to 2 hours. In addition, patients and their families need help overcoming the stigma of psychological evaluations.

- Feasibility: With proper planning, this research aim should be very feasible.

### 2.2. Health-related QOL

#### 2.2.1. Background

HRQOL is affected by physical well-being, mental state, degree of social support, effects of treatment, and the complications of a chronic illness. Several instruments, generic and IBD specific, are now available to measure HRQOL. For instance, the IMPACT-35 questionnaire developed by Anthony Otley, MD, MSc, FRCPC, and Anne Griffiths, MD, FRCPC, is a validated tool for children age 10 and older with IBD established for >6 months.

#### 2.2.2. Deficiencies in current knowledge

Reliable but flexible measurement tools are yet to be developed for use with young children with IBD. Plus, parental QOL has not been systematically studied. There are no studies assessing how QOL in the pediatric IBD population compares with that in children with other chronic illnesses. The relationship between QOL and disease activity needs to be better characterized. In addition, the impact of medications on QOL needs further study.

#### 2.2.3. Recommendations for research

- Aim 1: Prioritize how HRQOL in pediatric IBD compares with that in children with other chronic physical illnesses using developmentally appropriate and psychometrically valid measures.
- Aim 2: Standardize instruments used across studies.
- Aim 3: Add HRQOL as an outcome assessed in efficacy trials involving psychosocial treatments.
- Logistical support: Measures of HRQOL need to incorporate the disease course and phase of illness.
- Obstacles: None identified.
- Feasibility: The addition of HRQOL measures to existing studies of IBD outcomes is feasible and essential.

### 2.3. Psychosocial Issues

#### 2.3.1 Background

Children and adolescents with IBD have been reported to have several psychosocial difficulties in the areas of family conflict, peer-related socializing, and absences from school and extracurricular activities. Overall family dysfunction has been linked to greater IBD severity. Additional studies are needed to determine whether children and adolescents with IBD have a higher prevalence of anxiety and depression than children and adolescents who do not have IBD.

#### 2.3.2. Deficiencies in current knowledge

There is need for more systematic measurement of academic performance, family functioning, and social competence.

There is a need to focus on psychosocial adaptation to IBD and to identify factors that help predict which youth are at risk for difficulties in adjustment. Comparison studies with other illness groups are important. Prospective, longitudinal research to investigate developmental issues and their effects on adaptation to IBD are wanted. Finally, there is a need to consider psychosocial factors as moderators/mediators of the course and outcome of IBD.

### 2.3.3. Recommendations for research

- Aim 1: Identify which psychosocial factors are mediators and moderators of IBD course, outcome, and related QOL, with an emphasis on developmental differences between children and adolescents.
- Aim 2: Perform more comprehensive assessment of psychosocial problems using validated measures and multiple reporters.
- Aim 3: Perform studies that compare psychosocial factors in IBD with other chronic pediatric illnesses.
- Logistical support: Sociometric methods, using multiple reporters, provide reliable assessment of social functioning. This assessment needs collaboration with school systems and staff to travel to each participant's school. Trained staff is needed to watch and code videotapes of family functioning.
- Obstacles: Sociometric studies, billed as studies about friendships, are conducted without mentioning IBD or singling out a child. Nonetheless, there remains a concern that the child with IBD may be identified. Comparison of academic competence between schools needs to be standardized.
- Feasibility: With a properly trained staff, it should be very feasible to achieve the above aims.

## 2.4 Medical Compliance/Adherence

### 2.4.1. Background

Given that medications are a critical part of the management of IBD, medical adherence is particularly important. In other pediatric physical illnesses, the average adherence rates were only 50%, particularly during adolescence. Risk factors associated with lower adherence include disease remission, family dysfunction, and depression. According to the only study that has looked at adherence in youth with IBD, 48% of adolescents and 38% of parents reported being always adherent to all IBD-specific medications.

### 2.4.2. Deficiencies in current knowledge

Much work is needed to better understand psychosocial and developmental factors affecting medical adherence in children and adolescents with IBD. There needs to be greater focus on developing measures of medication adherence. The effects of medical compliance on medical and social costs to the family are understudied.

### 2.4.3. Recommendation for research

- Aim: Perform a study that more systematically identifies problems with adherence and associated effects on medical costs.
- Logistical support: Each study would need to include >1 measure of adherence such as electronic medication monitors, drug assays, and self-reporting. Additional staff would be needed for daily phone calls. Training would be needed for interviews.
- Obstacles: Electronic medication monitors and other equipment can be expensive and may malfunction. Studies of drug metabolites are costly, and the results depend on pharmacokinetics and the presence of stable, measurable metabolites.
- Feasibility: This research aim is very feasible if >1 measure of adherence is used.

## 2.5 Neuropsychiatric Aspects of IBD

### 2.5.1. Background

A growing body of literature suggests that at least some of the depressive symptoms observed in youth with IBD may be secondary to the direct physiological effects of IBD-related cytokines on the brain. Moreover, steroid treatments have been associated with emotional and cognitive symptoms in various populations, including youth with IBD. A recent study involving children (ages 8 to 17) with IBD found that subjects on high-dose steroids had poorer short-term memory and slower speed and reported more problems with working memory, flexibility, mood, and sleep compared with youth not on steroids.

### 2.5.2. Deficiencies in current knowledge

(1) Pain has been studied in youth with functional abdominal pain, but there is a deficit of such studies in the pediatric IBD population. (2) There is a need for genetic studies to find links between certain genes and psychiatric disorders or symptoms. (3) Longitudinal studies of steroid treatments are needed to examine the reversibility of emotional and cognitive disorders. (4) The effects of IBD-associated growth failure and pubertal delay on psychosocial well-being and social competence have not been investigated. (5) Brain imaging studies are needed to understand the neural substrates for depression and anxiety.

### 2.5.3. Recommendations for research

- Aim 1: Better differentiate between cytokine-induced versus steroid-induced emotional and cognitive symptoms compared with those unrelated to the IBD-inflammatory cascade or its treatment.
- Aim 2: Assess genetic interactions between IBD, irritable bowel syndrome, and depression and the interplay of genetic and psychosocial factors in predicting IBD course and related functioning.

- **Logistical support:** The measurement of cytokines and steroids is expensive, and utmost attention must be paid to appropriate tests of specificity and sensitivity of assays used and to the timing of blood draws. Preliminary work needs to be completed in defining subsets of psychopathological symptoms for IBD-related and independent origins.
- **Obstacles:** Many centers may not be equipped to provide such assays, and the addition into studies would require multisite collaboration. For genetic studies, it is important to identify a few target genes and link them to specific phenotypes, because a “shotgun” approach would be costly and probably unproductive. Brain imaging studies are expensive and must be performed at centers with trained personnel.
- **Feasibility:** With careful planning, such studies can be incorporated into existing studies of pediatric IBD, particularly those related to immune response.

## 2.6. Treatment/Prevention of Psychiatric/Psychosocial Dysfunction

### 2.6.1. Background

Several studies in adults with comorbid depression and physical illness have shown improved functioning after treatment with antidepressants. The role of antidepressants in children and adolescents, however, is less clear. Although many adolescents benefit from these medications, a small number of adolescents develop suicidal ideation. On the other hand, cognitive behavioral therapy (CBT) has the most empirical support in treating mild to moderate depression and anxiety disorders in youth without physical illness. CBT also has been shown to improve functioning in adolescents with various chronic physical illnesses.

### 2.6.2. Deficiencies in current knowledge

Many psychosocial treatment trials completed in youth with physical illness had small sample sizes and lacked a comparison condition. In addition, research is lacking in the following areas: (1) The development of treatment algorithms for different psychiatric symptoms or conditions; (2) longitudinal studies assessing treatment effectiveness over time and development; (3) mediators and moderators of treatment effects, including IBD-related and psychosocial factors; (4) the effects of treatment on areas such as social competence and medication adherence; (5) the effects of psychiatric treatment on IBD outcome or course, with associated medical costs; (6) the effectiveness of group therapy or support groups in preventing and treating psychosocial distress; and (7) resiliency or protective factors against psychiatric conditions in IBD compared with other chronic physical illnesses.

### 2.6.3. Recommendations for research

- **Aim 1:** Conduct randomized effectiveness studies comparing CBT with control conditions (with parental education or

- supportive therapy), with a focus on emotional and physical illness outcomes and the processes mediating treatment effects.
- **Aim 2:** Study mediators and moderators of treatment effects.
- **Aim 3:** Identify resiliency/protective factors in youth with IBD.
- **Logistical support:** (1) Psychotherapy treatment trials are costly and require appropriately trained personnel. (2) Sample sizes in the range of 60 to 100 subjects are needed. (3) Trained statisticians are required for such projects.
- **Obstacles:** Multisite studies will be needed to target adequate sample sizes. Careful coordination will be needed between behavioral specialists and the child’s medical team.
- **Feasibility:** With careful planning, it is very feasible to conduct research of behavioral interventions nested within medical care.

## 2.7. Proposed Study Aims

- 1) Identify risk and protective factors regarding depression, anxiety, and related psychosocial difficulties in young children and adolescents with IBD. These studies could include a focus on both biological and social factors to better understand the interactions between the brain, gut, immune system, and environmental influences.
- 2) Perform randomized treatment and prevention studies to reduce emotional suffering (anxiety and depression) and improve global functioning. Specific focus is needed on areas such as medical outcome, medical adherence, social competence, and QOL issues.

## 2.8. Issues Discussed

It was noted that CBT is a manualized intervention in which parents and children use a workbook. In addition, teaching videos and sophisticated measurements of adherence have been developed. Dr Szigethy has modified CBT specifically for children with IBD, in 3 main ways: (1) There is an emphasis on hearing the child’s narrative on how the illness affects that child. (2) There is a component that focuses on educating the parents about depression in IBD, family communication, and CBT techniques. (3) Training is provided for increasing social skills.

One complication about gauging the QOL of pediatric patients is that the reports of parents usually differ from those of their children. Parents usually perceive the QOL for their child as being worse than what the child perceives. It is therefore important to consider the reports of teachers and physicians as well. In addition, one needs to evaluate how well the children are functioning within their families, at school, and in extracurricular activities.

It is important to develop ways to offer psychosocial therapies to children living in less fortunate social circumstances who do not have ready access to the Internet and other resources for such therapies. Dr Szigethy has found that

cellular phones offer one way to conduct sessions with children in such circumstances.

It was recognized that there is an urgent need to train more therapists in using the CBT protocol and to study the efficacy of CBT in improving the mental health of children with IBD who are suffering from depression.

### 3. Epidemiology

Presentation by Devendra Amre, MBBS, PhD.

#### 3.1. Background

IBD is now cited as one of the 5 most prevalent gastrointestinal diseases in the United States. Many people affected by IBD develop symptoms before the age of 30 and have lifelong disease. Several recent studies strongly suggest that the prevalence of Crohn's disease and ulcerative colitis is rising in both developed and developing countries, among whites and nonwhites, and even among first-generation immigrants. In addition, preliminary data suggest an increase in the incidence of pediatric IBD, including a rise in incidence among minority children. Nonetheless, very little is definitively known about the cause of pediatric IBD.

To identify priorities for research, epidemiological studies were considered under 2 broad subdivisions: "descriptive" and "risk-factor" epidemiology. Studies in descriptive epidemiology look at the distribution of IBD in terms of whom the disease affects, when it occurs, and where it occurs. Risk-factor epidemiology includes the examination of 2 classes of risk factors: (1) diet and nutrition and (2) infections and hygiene.

#### 3.2. Deficiencies in Current Knowledge

The apparent rise in the incidence and prevalence of IBD suggests that environmental factors such as diet and infectious agents may influence the initiation, severity, or course of IBD in genetically susceptible individuals. Thus far, studies examining the roles of diet and infectious agents have focused mainly on adult-onset IBD. It is unclear whether the risk factors thought to play a role in adult-onset IBD can be directly extrapolated to childhood-onset IBD. For example, environmental factors such as oral contraceptive use and smoking may be less relevant to childhood-onset IBD.

Moreover, the existing tools to measure these risk factors are inadequate. It is difficult to ascertain a child's history of diet and infections except by retrospective studies. The Youth/Adolescent Questionnaire, developed in the Channing Laboratory at Harvard, is the only food-frequency questionnaire that has been validated among children, but it ascertains dietary information for just a 12-month period before application of the survey. It may take 3 to 5 years to design and validate a new questionnaire that targets specific risk factors for pediatric IBD. Thus, there are several limitations to performing risk-factor epidemiological analyses at this time.

When considering descriptive epidemiology, it is clear that a very limited number of studies have been conducted with North American pediatric populations to characterize the population-based prevalence and incidence of pediatric IBD and to describe the prevalence of specific IBD phenotypes, sorting them by age, region, race/ethnicity, gender, and so forth.

#### 3.3. Recommendations for Research

On the basis of the above considerations, this focus group recommended studying the distribution, frequency, and characteristics of pediatric IBD as the most important first step. After establishing valid prevalence and incidence data, we may know which risk factors to target. Answers to the following research questions would add to our knowledge and provide clues that lead to new interventions.

Is there an east-west gradient or north-south gradient in the incidence of pediatric IBD? If so, could it reflect differences in ethnic distribution? A Canadian study led by Charles Bernstein, MD, found that the incidence of IBD was higher in Nova Scotia and lower in British Columbia, corresponding to an east-west gradient.

Are there areas of higher prevalence in the United States? The Canadian study found various "hot spots" of IBD prevalence in parts of Manitoba. What are the reasons for these variations?

Is gender distribution of IBD in children truly the reverse of that found in adults? Male children have been observed to have a higher incidence of IBD. Are these differences the result of genetic or environmental factors or both?

Why is the highest incidence of IBD found in children older than 10 years of age? Is it related to latency? Do potential genetic or environmental risk factors play a role after this age? Are there protective exposures before age 10?

Why do ulcerative colitis and colonic Crohn's disease predominate in children younger than 8 years of age? Is this related to diet, infection, or bacterial colonization?

Are the frequency, disease course, and response to therapy in pediatric IBD similar among different ethnic and racial groups?

Does infection trigger or determine the severity and course of IBD?

#### 3.4. Proposed Research Actions

- 1) Investigate the burden of pediatric IBD and its distribution in the United States, in terms of:
  - (a) its incidence and prevalence; and
  - (b) its variation by geographic location, race, gender, and age.
- 2) Investigate the role of specific risk factors for pediatric IBD, namely:
  - (a) diet and nutrition; and
  - (b) infections and hygiene.

### 3.5. Logistical Support, Obstacles, and Feasibility

To achieve the above aims, we need a universal classification system for IBD, with clear definitions of such aspects as disease types, diagnosis, and location. CCFA has recently sponsored an initiative in this area. Second, we need a database for childhood-onset disease applicable to the US population. A major limitation is that there are no nationwide health information systems in the United States, and neither government health systems nor health maintenance organizations capture adequate pediatric IBD data. Some limited databases that could be used are the National Hospital Morbidity Database, National Health and Nutrition Examination Survey, Behavioral Risk Factor Surveillance System, and National Health Interview Survey.

If a nationwide study is too difficult to carry out, an alternate approach would be to select a few states that are heterogeneous, covered by a few insurance plans, and geographically distributed to represent the national population.

Whatever the approach, it will require the use of large databases and networking of different groups interested in such studies. Given that several networks studying IBD have already been established in various parts of the United States, it seems feasible to coordinate the work of these groups to conduct studies in the origin of pediatric IBD.

Once a study corresponding to the first study aim is completed, it will provide a baseline cohort for implementation of specific risk factor studies and lay a foundation for studying trends in disease occurrence over time.

### 3.6. Issues Discussed

CCFA has set up an epidemiology initiative that has had 2 phases so far. In the first phase, led by the Centers for Disease Control and Prevention, the rates of prevalence and incidence of IBD were calculated from the records of 9 regional health maintenance organizations covering a 30-month period. The results of that study will be published soon. The second phase, led by Kaiser-Permanente of Northern California and using the records in its database, will look at practice variations over a period of 72 to 76 months.

It was suggested that if Congress appropriates funds for an IBD action plan administered by Centers for Disease Control and Prevention, epidemiological surveillance would have to be part of the plan, and the pediatric age group could be added.

It was recognized that the role of risk factors, particularly diet and infections, needs to be investigated. Dr Amre's group is engaged in epidemiological studies both in North America and in developing countries such as India to determine which risk factors could play a role in IBD. Exposure information is being acquired through questionnaires and provincial prospective databases. Existing prospective databases in the United States could be tapped with suitable modifications

to assess these risk factors. Implementing truly prospective studies would be ideal but may not be logistically feasible unless high-risk cohorts could be identified for follow-up.

To perform a study of the incidence and prevalence of IBD in the United States, it would be important for researchers and pediatricians to form a collaborative network.

## 4. Microbiology

Presentation by Judy Splawski, MD.

### 4.1. Background

Numerous studies of IBD in humans and colitis induced in experimental animals have shown the intricate involvement of intestinal microflora in the pathogenesis of IBD. For instance, bacteria have been implicated in the stimulation of intestinal inflammation characteristic of IBD, and Crohn's lesions are most numerous in parts of the gut that are highly colonized. Genetically engineered mice deficient in immunoregulatory cytokines fail to develop spontaneous colitis when maintained in a germ-free environment, but they develop disease when their gut is subsequently colonized. In addition, antibiotics have been found to be effective as adjuncts to therapy for IBD.

The *NOD2/CARD15* gene, recently identified as a risk factor for Crohn's disease, codes for a bacterial pattern recognition receptor. In addition, Toll-like receptors on the gut lymphoid and epithelial cells have been found to promote or inhibit experimental colitis; these receptors also are involved in mediating the innate immune response to bacterial molecular patterns. Other studies have identified deficiencies of defensins, which are natural antibiotics, in cases of IBD.

### 4.2. Deficiencies in Current Knowledge

The deficiencies in our knowledge lead to a number of questions. For instance, are there specific bacteria or bacterial characteristics that initiate or perpetuate IBD? What bacteria and bacterial factors are important for the development and maintenance of tolerance to bacterial flora? If there are multiple insults from viruses, toxins, or food proteins, will they lead to breaks in the intestinal mucosa, exposure to bacteria, and loss of tolerance? Are there problems with the barriers set up by the host immune response? Or are there problems with the ability of the immune system to exert tolerance in the gastrointestinal tract? Is there a problem with the regulators of the immune response or in healing? How do children without IBD reestablish healing and tolerance after an initial insult?

### 4.3. Recommendations for Research

In light of the above background, this focus group identified a number of areas of study related to the behavior of bacteria and that of the host.

**4.3.1. Study aims related to bacterial behavior**

- Determine whether there are specific pathogens, groups of pathogens, or bacterial products that trigger an early seminal event in IBD.
- Identify specific proinflammatory features of the host response to the bacteria that are important for disease progression.
- Look for the potential for autoimmunity or molecular mimicry from the bacteria involved.
- Determine whether conventional treatment leads to changes in mucosa-associated flora or whether it simply hides the response.
- Examine the effects of probiotics in patients with a given IBD genotype.
- Determine the safety of probiotics in immunosuppressed patients, especially if they suffer from breaks in their mucosal barriers and defects in their ability to react to bacteria.

**4.3.2. Study aims related to host behavior**

1. Determine whether there are differences in mucosal immune function in response to infectious agents in IBD cases compared with controls.
2. Discover whether there is a loss of tolerance in normal children after intestinal infection and how tolerance is reestablished.
3. Determine whether, in cases of IBD, a deficient innate immune response leads to a more permanent, but destructive, adaptive immune response.
4. Look for defects in the activity of T-regulatory cells (CD4<sup>+</sup>CD25<sup>+</sup>FoxP3<sup>+</sup> T cells).
5. Identify specific host responses to bacteria that are detrimental and perpetuate the disease.
6. Determine whether genetic susceptibility has an impact on intestinal flora and the immune response to the flora.
7. Study the responses to stimulation of bacterial pattern recognition receptors in IBD cases and controls.
8. Develop better ways to study children with IBD on a long-term basis, seeking out the least invasive ways.
9. Perform long-term studies on infections, antibiotic usage, and food protein intolerance preceding the onset of IBD, especially in patients with a known genetic predisposition.

**4.4. Proposed Research Actions**

- Identify the microbes, antigens, and adjuvants that play an important role in pediatric IBD. This would include looking at initial colonization of the gastrointestinal tract shortly after birth.
- Use these reagents to test innate immune responses in pediatric IBD.
- Check the expression of bacterial pattern recognition receptors in early childhood, and clarify their role in pediatric IBD.
- Test the effects and mechanisms of action of probiotics in pediatric IBD cases.

**4.5. Logistical Support and Techniques**

To achieve the above aims, it will be necessary to establish a pediatric IBD database and to develop protocols that allow pediatric centers to evaluate, categorize, and treat IBD patients in a uniform manner. Some potential collaborators would be NASPGHAN and pediatric gastroenterology IBD consortia.

It also will be important to develop and use high-throughput techniques that allow researchers to do the following:

- Rapidly characterize the “microbiome” (full complement of microbes) in the intestines and fecal streams of healthy children and children with IBD.
- Characterize and standardize the collection, processing, and banking of gastrointestinal tissue biopsies obtained during clinically indicated endoscopy of children with IBD and controls.
- Identify host and environmental factors critical for the maintenance of normal gut microbiota.
- Assess the impact of genetic factors such as variants of the *NOD2/CARD15* gene on gut microflora.

**4.6. Issues Discussed**

It was noted that the tools are available to look at the intestinal flora of children and to determine whether the flora are different in IBD cases and controls. Characterization of the flora and bacterial pattern recognition receptors may be more clear-cut in children than in adults.

Once the intestinal mucosa becomes populated with bacteria, the flora remain stable over time. In addition, fecal flora are different from mucosal flora, and it is more important to study the latter because they appear to play a greater role in cases of IBD.

The intestinal microbiome is extremely complicated, and we are unable to culture most of the bacteria involved. The latest technology allows researchers to analyze bacterial ribosomal DNA, which circumvents the need to culture the bacteria. It was suggested that this approach could be used to analyze the child’s intestinal flora and to look at maternal input, particularly through breastfeeding. Using this technique, the group led by Charles Elson, MD, observed a shift in the intestinal flora of mice after induction of colitis, but the type of shift varied according to the method of induction.

The point was made that the immune system responds to a very limited set of antigens compared to the enormous number of potential targets. According to some estimates, microbial flora may have 2 to 4 million genes that could produce as many candidates for antigens. Yet, in the colitis models that have been studied, no more than 200 antigens appear to be involved in triggering an immune response in the host. It would therefore be important to focus on determining

how the host reacts to the mucosal bacteria and the role of that reactivity in IBD pathogenesis.

One area that needs to be explored is how the host response changes during early developmental stages such as in utero and shortly after birth.

## 5. Immunology

Presentation by Claudio Fiocchi, MD.

### 5.1. Background

Research over the past 3 decades has provided mounting evidence that an IBD patient's immune response is the fundamental process leading to intestinal inflammation and injury. Much of this progress is based on studies with cells and tissue samples obtained from adults with IBD and animal models of IBD. More recent evidence indicates that an abnormal interaction between the enteric commensal microflora and the intestinal immune system may underlie the initial pathogenic events of IBD. Until now, however, there have been just a few studies dealing with the immunology of pediatric IBD. As a result, investigation of the very early stages of the development of IBD has been missing.

There are several advantages of studying the immune response in pediatric IBD. In particular, young children with IBD are likely to represent a "virgin" population, in which intestinal inflammation has occurred during a relatively short time period and significant adaptive responses (such as tissue remodeling or fibrosis) have not taken place. These children therefore provide the opportunity to study the initial host-immune response and the long-term effects of using immunomodulatory drugs. These studies can reveal in greater depth differences in the immunological mechanisms between early and late disease such as the cytokine patterns in each disease stage. Ideally, immunological studies of early-onset disease may identify disease subtypes that require more intensive immunomodulatory therapy, leading to long-term benefits.

### 5.2. Deficiencies in Current Knowledge

The deficiencies in our current knowledge lead to several questions. For instance, how does pediatric IBD differ from adult IBD? Are immune abnormalities in pediatric IBD different from those in adult IBD? Why is poorly defined IBD (indeterminate IBD) more common in children than in adults? Is poorly defined IBD accompanied by fewer defined immune abnormalities? How do postnatal environmental challenges such as infections, vaccinations, antibiotic use, probiotic use, tonsillectomy, appendectomy, diet, and atopy affect the development of IBD?

## 5.3. Recommendations for Research

### 5.3.1. Immune system development

The systemic immune response of the neonate is highly plastic and can be manipulated to generate Th1, Th2, or other responses. In addition, little is known about the development of mucosal immunity in neonates such as how the mucosal immune system establishes a relationship with commensal bacteria and how it achieves and maintains tolerance to food antigens. Thus, research is needed to increase our understanding of intestinal immunity during normal development. This type of research will require the use of murine models. Some key questions follow.

- Does thymic education play a role in the development of IBD?
- Can plasticity of the immune response be used to educate or re-educate the mucosal immune system?

### 5.3.2. Genetics

Mutations in any of various genes of an IBD patient may disrupt homeostasis of the systemic or mucosal immune system. Two key questions are listed here:

- Do primary genetic defects that affect the immune system play a role in pediatric IBD?
- Do mutations in genes such as *NOD2*, *OCTN*, or *GLD5* affect the immune response in pediatric IBD?

### 5.3.3. Antigens

Various antigens have recently been postulated to induce disease. They include intestinal flora, specific bacterial and viral pathogens, dietary antigens, and self-antigens. Several questions can be raised here:

- What are the target antigens of the immune response in pediatric IBD?
- Are the target antigens the same as or different from those in adult IBD?
- Should dominant bacterial antigens be defined in pediatric IBD and compared with those of adult IBD?
- Can probiotics correct abnormal immune responses in pediatric IBD?

### 5.3.4. Innate and adaptive immunity

Innate immunity refers to relatively fixed, nonspecific responses of the immune system when first challenged by a new pathogen. Adaptive immunity refers to a more elaborate, secondary response, which can be cell mediated or antibody mediated. Children represent an ideal population in which to study the interactions between the innate and adaptive immune responses. Here are some key questions:

- Do primary abnormalities of innate immunity exist in children with IBD?
- Are there defects of antigen presentation by dendritic cells or other antigen-presenting cells in pediatric IBD?

- Are there abnormalities in the expression or function of Toll-like receptors in pediatric IBD?
- Should both antibody- and cell-mediated immunity be studied in children with IBD?
- Do children with IBD develop the same patterns of responses by Th1 and Th2 (T-helper cells) seen in adults?

### 5.3.5. Immunoregulation and tolerance

The presence of commensal bacteria plays a fundamental role in the development of normal systemic and mucosal immune systems. Children with IBD provide a unique opportunity to study the immune response to resident gut flora and early loss of tolerance resulting from perturbation of mucosal homeostasis. Key questions include the following:

- Are the mechanisms for the development of immune tolerance the same in children and adults?
- Do pediatric IBD patients have a defect in their ability to develop tolerance? How early does the tolerance defect develop?
- Are the mechanisms for the loss of tolerance in IBD the same in children and adults?
- Are T-regulatory cells quantitatively or qualitatively defective in pediatric IBD?
- Are defects in T-cell apoptosis present in children with IBD, as seen in adult patients?

### 5.3.6. Cytokines

It is critical to understand whether abnormalities of immunoregulatory and proinflammatory cytokines are the same in adult and pediatric cases of IBD. Studies of cytokine abnormalities in children can unravel the sequence of the inflammatory cascade. The results of these studies will have therapeutic implications. Key questions include the following:

- Are cytokines that initiate gut inflammation different from those that maintain it?
- Do they also differ between pediatric and adult IBD patients?

### 5.3.7. Mucosal barrier

The integrity of the intestinal epithelium is important for its function as an effective barrier that prevents spontaneous gut inflammation. Key questions are the following:

- Are alterations in the mucosal barrier primary or secondary to subclinical inflammation?
- Are defects in intestinal permeability and early immune response interconnected in pediatric IBD?
- Should pediatric IBD patients and their relatives be screened for abnormalities of intestinal permeability?

### 5.3.8. Immunity in early and late disease

Emerging evidence indicates that IBD develops in distinct phases when various mediators play differing roles.

Experiments with animal models indicate that different cytokines mediate inflammation during the early compared with late stages of disease, and the same cytokine can be protective in an early stage but pathogenic in a late stage. Some key questions are given here:

- Why is there a Th1-Th2 cytokine switch from the early to the late phase of experimental colitis?
- Why do some cytokines play aggressive and protective roles, respectively, in early compared with late IBD?
- Do children with early and late IBD produce different cytokine patterns?
- What are the therapeutic implications of a possible “phasic nature” of cytokine production in pediatric IBD?

## 5.4. Proposed Research Actions

- Study innate and adaptive immunity in pediatric IBD, and compare the immune response in early compared with late phases of IBD.
- Investigate the developmental aspects of mucosal immunity.
- Identify the target antigens of the immune response in pediatric IBD.
- Investigate the effects of therapy on the immune response in pediatric IBD.

## 5.5. Obstacles

- Lack of an NASPGHAN/ European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) position statement to integrate and facilitate research in pediatric IBD.
- Limited tradition of immunological studies in pediatric IBD.
- Limited track record of funding of pediatric gastroenterologists interested in IBD.
- Limited knowledge of the development of the gut from early life to adulthood.
- Limited knowledge of the development of gut flora from early life to adulthood.
- General resistance to the notion of routinely obtaining blood and tissue samples from pediatric IBD patients.

## 5.6. Novel Technologies

To achieve the above aims, it will be important to use some of the latest technologies to accomplish the following:

- Develop new animal models for experiments toward understanding the development of the normal intestinal mucosal system.
- Develop new animal models to follow the progression of gut inflammation according to antigen introduction and enteric flora acquisition.
- Use technologies to isolate and characterize dominant dietary and enteric bacterial antigens in children with IBD.
- Use genomics and proteomics technologies to study the immune response in animal models and children with IBD.

### 5.7. Logistical Support and Collaborations

- Develop a pediatric IBD network of investigators in NASPGHAN and ESPGHAN (the European counterpart of NASPGHAN), and organize a conference with them and others in Asia and South America, focusing on the mechanisms associated with gut immune development and pediatric IBD.
- Identify organizations supporting research in other chronic inflammatory/autoimmune diseases that show a surge in pediatric incidence, and organize a conference with them to compare mechanisms of immunity and inflammation.
- Educate investigators and institutional review boards about the importance of obtaining pediatric IBD samples.
- Develop a unified patient identification, assessment, management, and access network for pediatric IBD researchers.
- Create a centralized bank of pediatric IBD DNA, sera, and tissues that can be used for these studies.
- Develop systems to access pediatric IBD samples of blood, mucosa, and stools.

### 5.8. Issues Discussed

Some children develop protein-induced colitis, a non-IgE-mediated disease that appears clinically similar to IBD. The antigen that precipitates this event is most often milk or soy protein, but we do not understand the pathophysiology. In contrast to IBD, it does get better with time. This is a human model of IBD-like disease that would be worth investigating and comparing with IBD.

It was recognized that to understand the mechanisms of immune responses in early and late phases of IBD, experiments would need to be carried out on animal models. It would be important to determine the early responses of the animals to changes in the microbial environment.

Dr Kugathasan's group has shown that when treating pediatric IBD patients with infliximab, the duration of remission can vary, depending on whether the treatment was begun early after the appearance of the first symptoms (resulting in long-term remission) or after at least 2 years of disease duration (resulting in shorter remission). This raises the question of whether the changes in response are connected to the phase of disease development rather than to the patient's age. The answer to this question is not known. On a more general level, we do not know whether the immune response in pediatric IBD is truly different from that of adult IBD.

A recent article by Israeli investigators reports finding the anti-*Saccharomyces cerevisiae* antibodies marker in subjects up to 5 years before they developed Crohn's disease. This finding indicates that it would be important to identify similar immune markers before disease onset and to take steps to prevent the disease.

Children under the age of 7 rarely have the markers for the anti-*Saccharomyces cerevisiae* antibodies and antineutrophil

cytoplasmic antibody, perinuclear pattern. Therefore, looking for other markers for IBD would be worthwhile, especially for the younger age group.

The efficacy of probiotics is an area that needs to be explored. Probiotics may be better at preventing IBD than treating it. Some studies suggest that a person may get permanent colonization by probiotic bacteria if administered in the first 6 weeks of life. Thus, prevention of IBD may take the form of early colonization with probiotics or lifelong therapy. If probiotics indeed have beneficial effects in modulating the immune system, probiotic studies in infants and children should be conducted.

## 6. Quality Improvement and Safety

Presentation by Richard Colletti, MD.

### 6.1. Background

Health services research suggests that health care could perform a great deal better than it does today. An audit of medical records of a large sample of adults in 12 cities in the United States showed that only 55% of recommended care was being received by patients. Preliminary data collected by the Pediatric IBD Network for Research and Improvement indicate that there also is considerable variation in the care provided to pediatric IBD patients.

Variation in care can take the form of underuse, overuse, or misuse of diagnostic and therapeutic interventions, leading to lower quality of care, increased costs, and increased morbidity. Some variations are based on patient needs or preferences, but many are due to a lack of adherence by practitioners to best practices. Unnecessary variations can be reduced by moving toward standardization of care, which occurs when a network of physicians agrees to provide care in a uniform manner, using an evidence-based protocol of care appropriate for each patient.

The Chronic Illness Care Model of E.H. Wagner and coworkers provides a useful framework for developing changes to the system of IBD care. The model includes several components: family and patient self-management support, decision support, delivery system design, clinical information systems, community resources, and the healthcare organization. When this model (or a component thereof) was applied in caring for patients with asthma, congestive heart failure, depression, and diabetes, it resulted in significant improvements in clinical outcomes and QOL. In a study of 339 adults with IBD, when measures were taken to improve patient and family self-management, the results after 1 year showed a 38% reduction in clinic visits and a 19% decrease in hospital stays, and 10% more patients were in remission.

Medical safety is another important area that needs improvement. The monitoring and reporting of adverse events is an important part of medical safety and may be one of the most important aspects of treating pediatric IBD. Current reporting systems, however, have several pitfalls. In particular,

reports are filed sporadically and without knowledge of the proportion of patients who experience adverse drug reactions.

Thus, it is clear that quality improvement measures are needed to reduce variation in care and improve safety, leading to improved health outcomes and QOL.

## 6.2. Deficiencies in Current Knowledge

A structured literature review published in 2004 found “no hard evidence for change in disease outcome in Crohn’s disease during the last four decades.” This could mean that there has not been any improvement, or it could mean that we lack sufficient data. Despite the great advances in our scientific understanding of the disease and in therapies, we cannot be confident that new knowledge about Crohn’s disease has resulted in optimal patient care.

## 6.3. Recommendations for Research

This focus group proposed 2 major studies as follows.

- 1) Variation in Care: A prospective cohort study of variation in care of children and adolescents, beginning at the time of diagnosis of Crohn’s disease and continuing over 1 to 2 years.
- 2) Improvement Collaborative: Establishing an Improvement Collaborative to standardize methods of assessing growth in Crohn’s disease, identifying patients at risk for or with growth failure, and intervening to improve growth, including final adult height.

### 6.3.1. Variation in care study

The primary aims of the variation in care study are as follows:

- Characterize and measure the variation in care as currently practiced by a broad sample of pediatric gastroenterologists when treating pediatric cases of Crohn’s disease.
- Use variation in care data to identify diagnostic tests and therapies that may be underused or overused.
- Identify potential gaps between current care and recommended care.
- Use this project as a stepping stone to standardized care and randomized studies.

Using Web-based data entry, this study will involve computation of point estimates and standard deviations. It will look for correlations among physician and disease characteristics and diagnostic and therapeutic interventions. The variation in care data will be used to identify diagnostic tests and therapies that may be underused or overused and to identify potential gaps between current care and recommended care.

The variation in care study will measure a range of parameters:

- Patient characteristics: age, gender, ethnicity, race, and possibly epidemiological and genetic data.
- Physician characteristics: nationality and years in practice.

- Practice characteristics: private practice versus academic institution, use of an electronic medical record, treatment in a multidisciplinary clinic.
- Disease characteristics: the extent, duration, severity, and clinical course.
- Care delivery approaches: diagnostic testing and medication use.
- Adverse reactions to drugs.

### 6.3.2. Improvement Collaborative

An Improvement Collaborative in pediatric IBD will focus on growth and nutrition. It will have several phases.

- The first phase will involve selection of the topic and recruitment of faculty. The aims and measures will be defined and the tools created.
- The second phase will begin by enrolling participants from 15 to 20 practice sites. They will consult their patients’ records and share baseline data with other participants. They will meet in a learning session and discuss potential interventions for improvement in growth and nutrition. Back at their sites, they will test the interventions with small-scale, rapid-cycle experiments and check for improvements. They will then gather for another learning session, discuss their results and ideas, and return to their sites to test for additional improvements. Continuing this iterative process, they will come up with changes that result in improved care.
- In the third phase, information about the improvements will be disseminated to all pediatric gastroenterologists, who can then apply those advances at their own sites.

The primary aims of the Improvement Collaborative are the following:

- Increase the proportion of visits when growth and nutritional status are documented.
- Increase appropriate nutritional evaluation and intervention.
- Enhance parents’ knowledge of appropriate diet and the proportion of families who set self-management goals.
- Increase the proportion of children who are growing normally.

According to different studies, 36% to 88% of children with IBD have impaired growth, generally caused by undernutrition and the growth-inhibiting effects of cytokines. This results in significant deficits in adult height. Growth measures that can be used by the Improvement Collaborative would include growth velocity, height-for-age percentiles, height z scores, adjustments for midparental height, and weight and body mass index percentiles for age. Each site would also keep records indicating rates of detection and early intervention of growth delay.

The Improvement Collaborative will develop and test practical measurement and documentation tools. It will then look at potentially useful therapies such as dietary analysis and

counseling, patient and family self-management, supplemental oral feedings, nasogastric and gastrostomy tube feedings, and identification and treatment of ongoing inflammation.

#### 6.4. Proposed Research Actions

To improve the quality of care of children with newly diagnosed Crohn's disease, 2 studies are proposed, as mentioned above.

- 1) Variation in care study using a prospective cohort. This study is designed to identify underuse, overuse, and misuse of diagnostic and therapeutic interventions and to identify gaps between recommended and actual care so that the gaps can be closed.
- 2) Improvement Collaborative to improve nutrition and growth. This collaborative will work to continually improve the detection, treatment, and prevention of growth delay and growth failure in children with Crohn's disease. The effectiveness of the Improvement Collaborative will be evaluated by a prospective, randomized study with a comparison group (by either randomization or case-control) in which the results of sites completing the Improvement Collaborative approach will be compared with results from other sites performing care as usual.

#### 6.5. Novel Technologies

The technology of improvement science will be used to carry out the Improvement Collaborative. Application of this technology will be relatively novel for cases of IBD. In addition, Web-based technology will be used for data collection and reporting and other communications.

#### 6.6. Logistical Support and Collaborations

The Improvement Collaborative will involve 15 to 20 practice sites communicating electronically and at 3 face-to-face meetings. The Web-based system will require multisite database management, including data collection, storage, validation, and analysis. This proposed project would ideally be a collaboration of CCFA, NASPGHAN, the American Board of Pediatrics, and the American Academy of Pediatrics.

#### 6.7. Obstacles and Feasibility

Feasibility of the proposed projects has been demonstrated by Pediatric IBD Network for Research and Improvement and by earlier projects in other fields. An infrastructure for cohort studies has been created, and the design phase of the Improvement Collaborative is largely completed.

#### 6.8. Issues Discussed

What should be the benchmark for success in treating patients with IBD? In the case of pediatric IBD, one indicator is growth. In the clinic, physicians also can use the Pediatric Crohn's Disease Activity Index to gauge the patient's pro-

gress. There also is a pediatric IBD quality-of-life questionnaire called IMPACT-35, mentioned earlier.

It was pointed out that before a particular standard of care is written up, there needs to be evidence to support those recommendations. Currently, such data are lacking. The proposal here, however, is to evaluate variation in care as a step that would potentially lead to standardization of care. We may not have enough evidence to write an algorithm for any patient from start to finish, but initial best practices can be developed based on the evidence and expert opinion.

The Improvement Collaborative would be a systematic method of improving documentation of growth and evaluating interventions to improve growth. Through an iterative process using the improvement model, changes in care delivery that lead to better growth can be identified and tested. Effective changes can then be disseminated to all pediatric gastroenterologists who care for children with Crohn's disease.

### 7. Pharmacogenomics

Presentation by William Faubion, MD.

#### 7.1. Background

Pharmacogenomics is defined as the study of the effects of genetic polymorphisms on the body's responses to drugs. It is based on the principle that variations in response to a certain drug, as observed in a population, reflect functional differences caused partly by variant alleles of the same gene.

Factors affecting drug responses can be placed in 2 categories:

- 1) Pharmacokinetic factors, which determine drug concentrations as a function of time and dosage. These factors affect drug absorption, distribution, metabolism, transport, and excretion.
- 2) Pharmacodynamic factors, which regulate the body's response to a certain drug at a fixed concentration. These factors affect such processes as receptor binding and signaling pathways.

Pharmacogenomics research is important for pediatric cases of IBD for several reasons. For instance, the efficacy of various drugs in treating IBD has been established, but toxicity and lack of response are serious problems, especially in pediatrics. Drug reactions have been estimated to be the fourth leading cause of death in the United States. Also, the pediatric population has a relative lack of confounders such as comorbidities or the use of concomitant medications. In addition, there may be age-dependent gene expression that is uniquely important for pediatric IBD.

#### 7.2. Translational Research Strategies

The earlier strategy for translational research in pharmacogenomics focused on identifying 1 or a few SNPs in a single candidate gene. An example is the gene for the enzyme thiopurine methyl transferase (TPMT), which is

involved in the metabolic pathway for the drug 6-mercaptopurine, classified as a thiopurine. 6-Mercaptopurine is an immunosuppressant used to treat IBD.

The new strategy is to seek out SNPs in many genes in the candidate pathway for a given drug or set of drugs. Each gene may have  $\approx 5$  to 10 SNPs, and up to 50 genes are genotyped per pathway per subject. This would add up to 500 SNPs per pathway per subject. The pathway for thiopurine metabolism is a good example of a candidate pathway that has been well worked out. It should be noted that modern studies of SNPs are done by looking for optimal subsets of SNPs, known as haplotype-tagging SNPs.

If a candidate pathway has not been worked out, the strategy is to perform genome-wide scans to search for chromosomal areas that show linkage to a drug response phenotype (such as an adverse reaction or efficacy). After that, specific candidate genes in these areas have to be identified. This strategy extends and complements the candidate pathway approach but is far more expensive.

The pharmacogenomics approach has been applied successfully in identifying polymorphisms in several genes:

- Genes for the enzymes CYP2C9 and VKORC1, which are involved in the metabolism of warfarin, a drug widely used to inhibit the synthesis of blood clotting factors.
- The gene for epidermal growth factor receptor, involved in the action of gefitinib, a drug used to treat breast cancer and lung cancer.
- The gene for TPMT, involved in thiopurine metabolism.

Pharmacogenomics methodology can help address 2 major questions:

- 1) Why do patients develop drug-related toxicity? Many patients with thiopurine-induced myelosuppression have normal TPMT alleles. This implies that many patients with normal TPMT may have polymorphisms in genes related to other parts of the thiopurine pathway. An auxiliary question is whether complications of therapy such as pancreatitis are predictable.
- 2) Does genetic variation in pharmacokinetic/pharmacodynamic pathways predict drug responsiveness? If so, are we getting close to individualized therapy? We know that 12% to 20% of patients do not respond to corticosteroids and that 40% of patients do not achieve remission with anti-tumor necrosis factor (TNF) or TNF inhibitor therapy. Can we predict this before using potentially toxic immunosuppressive therapy?

### 7.3. Recommendation for Research

This focus group proposed applying the candidate pathway approach to study the thiopurine pathway in pediatric patients selected prospectively and assaying polymorphisms predictive of toxicity and/or response. These studies can be performed with the modern technology of

high-throughput genotyping using haplotype-tagging SNPs for known thiopurine candidate pathways.

### 7.4. Feasibility and Logistical Support

The feasibility of the study would depend on the number of patients needed and the cost. If a polymorphism is relatively rare, fewer patients are needed to study it, but if the allelic variation is common, many more patients are needed. To study the thiopurine pathway, between 500 and 800 patients would be needed. There are  $\approx 20$  different genes involved in the thiopurine metabolic pathway. If one assumes that there are 10 polymorphisms per gene, it means one would be genotyping  $\approx 200$  SNPs per patient. The cost of genotyping, at the rate of 3 to 5 cents per SNP, would come to \$6 to \$10 per patient. For 500 patients, the cost of genotyping would total \$3000 to \$5000. In addition, there would be administrative costs at each center. Thus, cost-wise, the study would be very feasible. To make the study feasible in terms of patient numbers, a pediatrics IBD pharmacogenomics research consortium would be needed.

### 7.5. Issues Discussed

One of the confusing issues is that different studies have used different clinical end points. To compare patients' responses (including toxicity and lack of response) to a given drug, we need firm, well-defined end points. A second issue is when to test the patient's response, because the time of response can vary greatly. To study the thiopurine pathway, the patient needs to be on a defined dose of therapy for at least 4 months before the response can be adequately assessed.

To correlate the genetic results with clinical outcomes, it is imperative to measure the drug levels. In this respect, studying the thiopurine pathway is attractive because we can measure drug levels and look at pharmacodynamic factors unrelated to drug levels but related just to the response of target genes.

Perhaps it is more important to check the enzyme activity (phenotype) than to determine SNPs (genotype). This raises the question of what factors affect enzyme activity. Would they be polymorphisms within the gene for that enzyme or in upstream or downstream genes? These factors need to be clarified.

Corticosteroid metabolism pathways also have been well worked out and can be studied by the candidate pathway approach. Many pediatricians, however, would like to move away from the use of corticosteroids.

Genotyping is not so expensive if the study looks at 20 to 50 genes in a candidate pathway, as noted above. Genome-wide scans, however, can be really expensive. It costs about \$1200 per sample for the Affymetrix 500K SNP chip, and the sample size can be as high as 1000. In addition, even when the cost of genotyping is low, there are significant costs associated with conducting a rigorously controlled, prospective study.

Other drugs that may be considered for study would be steroids and TNF inhibitors (anti-TNF drugs). It would be

important to determine why some patients are steroid dependent while others are steroid refractory. TNF inhibitors have shown a lot of promise in reducing surgery and hospitalization, yet 30% to 50% of children either do not respond or lose response. A candidate pathway for TNF inhibitors, however, has not been worked out, and their anti-inflammatory effects appear to be extremely complex.

The thiopurine pathway is a very good choice for an initial study because so much is known about it. Once it is carried out and its feasibility is demonstrated, a larger net needs to be cast to look for additional alleles involved. We may get more of a gene-based understanding of the development of IBD.

## 8. Nutrition and Diet

Presentation by Anthony Otley, MD, MSc, FRCPC.

Diet has a significant influence on the environment of the intestinal epithelium, and nutrition has been cited as a potentially significant contributor to the pathogenesis of IBD. In treating patients with Crohn's disease, many centers use nutritional therapy as a primary (first-line) therapy. Discussion focused on 3 areas: diet and epidemiology of IBD, efficacy of enteral nutrition as primary therapy, and mechanisms of action of enteral nutrition.

### 8.1. Diet and Epidemiology of IBD

#### 8.1.1. Background and deficiencies in current knowledge

Numerous nutritional components have been considered as possible factors influencing the pathogenesis of IBD. They include simple sugars, proteins, fats, total calories, and cow's milk protein. Methodological limitations of these studies, however, make it difficult to reach any conclusions about the relationship between dietary components and the origin of IBD. On the whole, no particular nutrient has been identified as a trigger for IBD.

#### 8.1.2. Limitations in data collection methods

There are 4 general methods for assessing dietary intake of individuals in observational studies: diet history, food frequency questionnaires, diet diaries, and 24-hour recalls. Each method has its strengths and limitations.

Diet histories and food frequency questionnaires both rely on the patient's recall of past diet, which is particularly problematic for children. Food diaries provide a good estimate of food and nutrient intake on the days measured, but they record current intake, which may not reflect preillness diet. Dietary assessment by multiple, random 24-hour recalls is most advantageous for measuring "usual" dietary intake. Some recall is required, and it is often difficult to contact individuals and obtain their recall on random days.

In studies in which dietary data are collected after diagnosis of IBD, there are several potential threats to validity: Association between a dietary factor and disease may reflect an

adaptation to rather than the cause of the disease; there is a potential for recall bias among patients who may have preconceptions about the association of certain foods with IBD; and accurate recall of dietary intake is difficult, and poor recall may occur by all study subjects.

#### 8.1.3. Recommendations for research and feasibility

*Proposal 1.* Determine the nutritional risk factors for the initiation of IBD among a baseline population-based registry of unaffected individuals or unaffected relatives of IBD patients. Population-based registries would provide invaluable information but would require enormous sample sizes. For a pediatric study of a population of unaffected individuals, if the incidence of IBD is 1 to 4/100,000, one would need a cohort of between 0.6 million and 2.4 million individuals. In addition, the costs would be high, and sufficient time would be needed for longitudinal follow-up. For a study of a population of unaffected relatives of IBD patients, the sample size would not be as large but would still be significantly high. Additional obstacles would include costs and follow-up time. As a result, such studies currently are probably not feasible.

*Proposal 2.* Determine the nutritional risk factors for the progression or recurrence of activity of IBD among affected patients in remission. It is hypothesized that dietary factors influencing the recurrence of IBD would enlighten us about the factors involved in the initiation of IBD. In this case, the sample sizes are more attainable than in the first recommendation. One limitation here is that patients might modify their diet on the basis of their symptoms. Another concern is that the study would require the coordination of efforts between multiple existing registries or cohorts. Plus, because it is unknown whether factors that initiate IBD are the same as those that trigger a flare, one might question the importance of the results. On the whole, this proposal has significant limitations.

### 8.2. Efficacy of Enteral Nutrition as Primary Therapy

#### 8.2.1. Background

Enteral nutrition is regarded as first-line therapy for pediatric Crohn's disease in various centers in the United Kingdom and other parts of Europe and Canada. It has been found to be an effective alternative to corticosteroids in the treatment of active Crohn's, although its likelihood of inducing clinical remission appears to be lower than that of steroids.

Exclusive enteral nutrition (EEN) can induce remission of active Crohn's disease, maintain remission of the disease, achieve mucosal healing, and improve HRQOL. It is not simply "nutritional repletion" or "gut rest." Open trials in children have documented endoscopic healing and decreased mucosal cytokine production after EEN therapy.

#### 8.2.2. Deficiencies in current knowledge

A number of questions still need to be answered. For instance, what is the place of EEN in the therapeutic

armamentarium? Why is EEN not used more widely in treating Crohn's disease? Is there a role for EEN specifically at the time of first presentation of Crohn's disease? What is the optimal duration for EEN treatment, and what is the optimal way to reintroduce normal diet after the period of EEN? What subgroup of patients should be managed with EEN? How can compliance with and tolerance of EEN be optimized? What are the medium- and long-term effects of EEN on nutrition, bone nutrition, and growth? Does treatment at the time of first presentation modify subsequent disease course?

### 8.2.3. Recommendations for research and feasibility

*Proposal 3.* Explore the reasons for variations in the use of enteral nutrition as primary therapy.

Some questions to answer would include these: Why is EEN not used more widely? Is it because of lack of a proven mechanism of efficacy? Is it because of lack of resources? Are there societal/cultural factors at play? Is it primarily patient-driven or physician-driven resistance?

This study would require coordination of multiple sites within and between countries, but it is very feasible and important.

*Proposal 4.* Conduct randomized, controlled trials of EEN. Two possible studies are given here:

- a) Randomization of subjects to receive 1 of 2 EEN regimens of varying lengths, with primary outcomes being rate of induction of remission and maintenance of remission for possibly the first 2 years after diagnosis.
- b) Comparison of a group randomized to receive EEN alone with a second group receiving EEN and immunosuppressive therapy, with elucidation of remission rates and long-term disease behavior.

Additional outcomes of these studies would include examination of QOL markers, nutritional markers, bone turnover markers, linear growth, and pubertal development.

For any of these types of trials, the sample size would need to be large. Given the infrequent use of EEN at many American centers, each study would need to involve centers in Canada, Europe, and Australia, as well as the United States. Participating centers would need to agree on a standardized approach for the EEN therapy they use. Such clinical trials are feasible, and the questions raised are important, but they may need to await the results of proposal 3 before being undertaken.

*Proposal 5.* Establish a registry of EEN patients to determine the natural history of this therapy and to compare it with other therapies.

Such a study would address questions such as, Does EEN treatment at first presentation alter subsequent disease course? Such questions may best be answered by using a prospective patient registry.

This study would need to include patients receiving other types of therapies also to compare the disease course

across therapies. It would need to include pediatric IBD cohorts/registries in North America and Europe, and they would need to adopt standardized data collection tools. Once the appropriate infrastructure is in place, such an endeavor should be achievable.

## 8.3. Mechanisms of Action of Enteral Nutrition

### 8.3.1. Background and deficiencies in current knowledge

The mode by which enteral nutrition induces control of intestinal inflammation remains unknown. Several mechanisms have been proposed, including (1) provision of "bowel rest"; (2) enhanced nutritional status and provision of important micronutrients to the diseased intestine; (3) correction of abnormal intestinal permeability; (4) reduction of antigenic load; (5) alteration in intestinal microbial flora; and (6) immunological downregulation. Growing evidence suggests that the intestinal epithelium modifies the immune response according to the luminal environment. The most likely mechanisms are alteration of gut flora, modulation of epithelial responses, and direct anti-inflammatory effects. These may act in combination.

Various nutrients have been studied for their influence on the efficacy of EEN therapy. For example, studies with lipids in rodent models of colitis have shown that feeds enriched with n-3 long-chain polyunsaturated fatty acids (n-3 PUFAs) consistently reduce intestinal inflammation. In addition, medium-chain triglycerides may also exert an anti-inflammatory action. A clinical trial showed that a diet enriched with n-6 PUFAs gave significantly higher rates of remission of Crohn's disease than a diet enriched with monounsaturated fatty acids. There remain, however, major gaps in our understanding of the mechanisms by which lipids influence mucosal inflammation.

### 8.3.2. Recommendations for research and feasibility

*Proposal 6.* Define the mechanisms of action of EEN in the treatment of active Crohn's disease. This study may include investigating the mechanism of action of lipids.

Several general aims can be outlined:

- Understand the effects of diet on epithelial cell activities and especially on the intestinal epithelium.
- Describe the nature of gut microflora in normal and disease settings and as a consequence of EEN in IBD.
- Include studies in vitro, in animal models, and in human subjects to answer various gaps in knowledge.

Novel technologies useful here would include nutrigenomics techniques, temperature-gradient gel electrophoretic analysis of bacterial 16S ribosomal DNA, and polymerase chain reaction.

Logistical support would be needed from formula companies and individuals with expertise in various fields, including microbiology, molecular biology, cell biology, and immunology.

Researchers would need to address concerns that changes in gut microflora could be a reflection of decreased inflammation rather than a specific result of EEN.

This type of study is very feasible because appropriate technologies are available or adaptable, because known methods can be used for work in vitro and with animals, and because human subjects can be tested either in pilot work to investigate novel hypotheses or as part of a clinical trial to assess the efficacy of a new EEN formula or treatment regimen.

#### 8.4. Proposed Research Actions

- Define the mechanisms of action of EEN in the treatment of active Crohn's disease. (This item corresponds to proposal 6 above.)
- Establish a registry of EEN patients to determine the natural history of this therapy and to compare it with other therapies. (This item corresponds to proposal 5 above.)
- Explore the reasons for variations in the use of enteral nutrition as primary therapy. (This item corresponds to proposal 3 above.)

#### 8.5. Issues Discussed

There appear to be a number of reasons why EEN therapy is not widely used in the United States:

- No randomized, controlled trial against placebo has been carried out.
- Generally, steroids are more efficacious. For pediatric patients, however, EEN offers efficacy and benefits on growth. This may be the reason why EEN is used more in treating children than in adults.
- Setting up the infrastructure for EEN therapy is a big limiting factor. Centers need to be set up with a nutritionist, a learning center (to learn how to insert the nasogastric tube), and a social worker to provide EEN.
- Most pediatricians in the United States are not aware of the efficacy of EEN.

As with other treatments, EEN may be used in combination with other therapeutics such as steroids, immunomodulators, and biologics. The choice of therapies (or combination) depends on how the patient responds. EEN alone does not work for everybody.

To determine outcomes of EEN therapy, it will be important to have a registry and to follow large numbers of patients prospectively accumulated.

Outside the United States, some patients who started with EEN during childhood wish to continue with it in adulthood. Within the United States, however, EEN is rarely used in adults. It seems that much depends on the environment in which this therapy is administered.

Endoscopic examinations of patients before and after treatment with EEN have revealed mucosal healing in a significant number of the patients. Other studies have shown decreased mucosal cytokines.

Unlike a host of other therapies, EEN does not have immunosuppressive side effects. In addition, a patient who is on EEN can avoid taking steroids. On the other hand, the psychological effects of prolonged EEN therapy have been poorly studied.

It would be important to determine the particular subgroups for whom EEN is more likely to be effective. Perhaps one needs to check the genotype and phenotype of the patient to target the therapy that would have the best effect. Patients with certain genotypes and phenotypes may not respond to EEN.

## 9. Growth and Skeletal Health

Presentation by Francisco Sylvester, MD.

Growth and bone development are intimately intertwined areas, but for the purpose of this report, they were considered separately.

### 9.1. Growth in Children with IBD

#### 9.1.1. Background

Growth is a good indicator of the health and well-being of a child. It is often impaired in children with IBD, especially Crohn's disease. One major reason for growth impairment is lack of adequate nutrition, which in turn can result from decreased intake, increased needs, increased enteral losses, and altered nutrient utilization. Nutrient deficiencies may have direct effects on the growth plate and other tissues. Additionally, immune factors such as cytokines can affect growth directly and indirectly by affecting key hormonal axes such as the growth hormone/insulin-like growth factor I (GH/IGF-I) axis and adrenal steroids. Consequently, growth of tissue compartments is compromised, and skeletal and sexual maturation is delayed.

Appropriate anti-inflammatory therapy and nutrition can help overcome growth failure and restore pubertal progression, but these measures are not always successful, and some children with IBD become permanently stunted. Moreover, it is not clear whether normal body composition can be achieved in children with IBD with current therapies.

#### 9.1.2. Deficiencies in current knowledge

We know that multiple factors related to nutrition and the immune system are involved in retarding growth in children with IBD, but the precise mechanisms by which they act are not fully understood. In addition, we have yet to identify the best therapies that would ensure optimal growth, and we do not have a good understanding of who is at risk for not achieving predicted adult height.

#### 9.1.3. Recommendations for research

In formulating recommendations for research, the overarching theme was to understand the basic physiological

disturbances caused by IBD on growth and pubertal development in children.

*Proposal 1.* Understand the availability and utilization of nutrient substrates necessary to achieve normal growth, body composition, and progression through puberty.

Initial studies can look at concentrations of particular substrates in serum or tissue samples. If deficiencies are identified, the next step would be to monitor the degree of response to supplementation with respect to linear growth, weight gain, body composition, and pubertal development.

Appropriate technologies are available to determine nutrient flux and body composition. It would be useful to adopt multidisciplinary approaches (clinical and laboratory) and to test hypotheses in animal models.

In working with children, sample size may need to be large, as children at different stages of pubertal development may have unique requirements. Participating centers would need to adopt standardized techniques.

One limitation is that only a few nutrition laboratories have access to the mass spectrometric equipment needed for mineral kinetic studies.

*Proposal 2.* Better understand key endocrine abnormalities in children with IBD and identify the significant determinants of those most at risk. These include the GH/IGF-I axis and adrenal steroids. Children need to be carefully assessed for progression of puberty by personnel familiar with sexual maturity staging (Tanner staging). After that, significant determinants would need to be identified so that mechanistic studies can be undertaken. Animal models could provide valuable information on the disturbances of endocrine axes and target gene responses. Hormone assays are often costly and may be more difficult to interpret for hormones exhibiting pulsatile secretion. Tissue concentration of hormones will require tissue biopsies.

*Proposal 3.* Study the efficacy of treatment modalities used to treat IBD in children on growth and body composition, including pharmacological and nutritional therapies.

Data need to be collected prospectively from the time of diagnosis of IBD, with adequate tracking of medications used. Additionally, data will be needed on linear growth, weight gain, body composition, bone mineral content, and bone remodeling markers at defined intervals to establish correlations. This study will require dedicated coordinators or telephone systems for medication tracking over extended periods. Sample size will need to be large, requiring multicenter collaborations with standardized data collection techniques.

## 9.2. Skeletal Health in Children with IBD

### 9.2.1. Background

There are fundamental physiological differences between pediatric and adult skeletons. In adults who have

achieved peak bone mass, there is a process called bone “remodeling” involving bone formation by osteoblasts and bone resorption by osteoclasts in response to stress or trauma to bone. These activities are coupled, so bone mass remains stable until women reach menopause and men reach older age, when bone formation can no longer keep up with bone resorption. This results in progressive bone loss. Although bone remodeling is active in growing children, the main process is bone “modeling,” in which bone formation and resorption occur simultaneously, resulting in net bone formation and reshaping. Young people normally achieve complete bone growth in their late teens and reach peak bone mass in their early twenties.

Nutritional and immunological factors play key roles in bone modeling and remodeling. Nutritional factors include calcium, vitamin D, protein and caloric intake, vitamin K, and micronutrients. Immunological factors include T cells and cytokines. In addition, inactivity and decreased lean tissue mass appear to affect bone development.

Given the above differences, it is likely that the effect of IBD on skeletal health differs between children and adults. Therefore, interventions to improve bone mass and to reduce fracture risk will need to be designed specifically for children.

### 9.2.2. Deficiencies in current knowledge

We need to explore the natural history of the effects of IBD on bone health and development, particularly in children, and to elucidate the mechanisms involved. In addition, we need to evaluate fracture risk in pediatric cases of IBD. Do children with IBD fracture at a higher rate than normal children? Are they more susceptible to fracture during childhood or when they are older? Furthermore, we need to evaluate how the therapies used for pediatric IBD affect bone health. We also need to determine the best method to assess skeletal health in children.

### 9.2.3. Recommendations for research and feasibility

In formulating recommendations for research, the overarching themes were the impact of IBD on skeletal health in children and adolescents, interventions to optimize skeletal health, and bone cell function in children with IBD. *Proposal 4.* Understand the natural history of bone mass accrual and bone structure in children with IBD, and differentiate between decreased bone accrual and increased bone loss. A comprehensive “bone history” would help determine the history of osteoporosis and other risk factors that are independent of IBD in first-degree relatives. Two technologies, dual-energy x-ray absorptiometry and quantitative computed tomography, can be used to monitor bone mass. Hormone concentrations, nutritional measures, growth factors, cytokines, and inflammatory markers will need to be followed up prospectively. Fractures will need to be recorded

and characterized on the basis of the causative trauma. There is, however, no ideal method to measure bone mineral density, bone structure, and bone mechanical properties in children. Currently available techniques have significant limitations. Determining fracture risk will require long-term follow-up. Because vertebral fractures may be asymptomatic, the children will require imaging of the spine. Centers equipped with both dual-energy x-ray absorptiometry and peripheral quantitative computed tomography will be particularly suited to perform these studies. It will be important to use comparable scanners and pediatric software.

**Proposal 5.** Test the best approaches to optimize bone mass in children with IBD so that they can reach their genetically determined peak bone mass. Bone anabolic measures need to be tested, including control of inflammation, nutritional factors (such as calcium and vitamin D), and weight-bearing activity. The natural history of bone development in children with IBD will need to be understood before intervention trials are performed.

Trials will need to involve multiple centers because large sample sizes will be required. Ethical issues related to the use of placebos and the uncertainty of optimal dosing will need to be worked out. Maintaining adherence in physical activity or nutritional interventions may also be issues. Because the risk of fracture for children with IBD is unknown, changes in bone mineral density may serve as a surrogate but imperfect end point.

**Proposal 6.** Define changes in bone modeling and remodeling associated with IBD in children. Stable calcium isotopes may be used to gain insights into calcium utilization, including incorporation and release from bone. This approach would be useful in assessing rates of bone calcium deposition across puberty compared with normative data and can help target the component of calcium flux that is most affected by the disease process. This approach also would be efficacious in addressing mechanisms of the action of drugs used to affect bone turnover and accretion. The effects of different cytokines can be studied using established culture models for osteoblasts and osteoclasts. Bone biopsy data, using a technique called dual tetracycline labeling, will be needed, especially at the time of diagnosis. Animal models of chronic intestinal inflammation can be used to determine its effects on bone. Biochemical markers can give some hints on remodeling.

There are, however, ethical issues related to performing bone biopsies for histomorphometry and obtaining cells from children with IBD if there is no direct or potential benefit for the child.

### 9.3. Proposed Research Actions

- Understand the availability and utilization of nutrient substrates necessary to achieve normal growth, body composition, and progression through puberty.

- Better understand key endocrine abnormalities in children with IBD and identify the significant determinants of those most at risk. These include the GH/IGF-I axis and adrenal steroids.
- Study the efficacy of treatment modalities used to treat IBD in children on growth and body composition, including pharmacological and nutritional therapies.
- Understand the natural history of bone mass accrual and bone structure in children with IBD and differentiate between decreased bone accrual and increased bone loss.
- Test the best approaches to optimize bone mass in children with IBD so that they can reach their genetically determined peak bone mass.
- Define changes in bone modeling and remodeling associated with IBD in children.

### 9.4. Issues Discussed

In evaluating fracture risk in children with IBD, it will be important to check for clinically silent vertebral fractures. It also will be useful to examine fracture risk in adult IBD patients who were diagnosed during childhood. Vertebral fracture assessment with the newer bone scans can help reveal vertebral shape and deformity and subclinical fractures. Several studies have looked at clinically obvious fractures. One of these studies, led by Dr Charles Bernstein in Canada, showed a 40% increase in fracture rate compared with the general population. It is now important to look for vertebral fractures that are not clinically obvious because after the first fracture, the risk of a second fracture increases.

Bone immunology, or osteoimmunology, is another important area to investigate. It might lead to the discovery of surrogate markers that help identify patients at risk for osteopenia, new ways of preventing osteopenia, and ways to assess the effects of therapy.

New studies are needed to clarify the role of vitamin D in promoting growth and bone health. Besides its role in mineral metabolism regulation, vitamin D has anti-inflammatory properties and is involved in immune regulation and cancer prevention. There are many reasons why children with IBD may have inadequate stores of vitamin D.

We need to give high priority to investigating how current therapies affect growth. Here, we have a great opportunity to study patients while they are undergoing therapy to investigate the mechanism of action of the therapy and to examine the incidence of fracture and bone thinning.

Prepubertal male children are more at risk for growth failure than female children, but the mechanisms await elucidation.

The role of genes in influencing growth also needs to be studied. Some data indicate that insertion/deletion mutations in the *NOD2/CARD15* gene are associated with growth failure.

The issue of using IGF-I in treating IBD-affected children experiencing growth failure needs to be investigated.

The Food and Drug Administration recently approved the use of IGF-I therapy to treat children who are resistant to GH. In children with IBD, however, IGF-I deficiency is transient; it corrects itself during therapy. Studies on malnutrition indicate that the level of IGF-I declines with fasting in 28 hours, but the serum level increases when nutrients are restored.

Should children with growth failure be treated with GH? To date, there have not been any large, randomized trials of GH in pediatric IBD, only a few with fairly small numbers of cases. Most children have sufficient GH, but they do not have the nutritional and immunological environment by which it can be used and IGF-I can be generated. Therefore, it may be better to try nutritional therapy before using GH therapy for a child experiencing growth failure. The effects of GH need to be studied in a randomized, controlled trial.

When we study how IBD affects bone health, we will probably find mechanisms that are unique to children. IBD is likely to affect the adult and pediatric skeletons differently, so bisphosphonates or other antiresorptive therapies that work in adults with bone loss may not be the best choice for children.

We need national, collaborative studies that look at the effects of Crohn's disease on bone health not only in the pediatric patient at the time of diagnosis but also on the effects on bone when that patient is 25, 35, and 45 years of age. Such studies would help define the problem and indicate changes needed for the care provided.

Pediatric gastroenterologists may benefit greatly from collaborations with pediatric endocrinologists to address issues of growth and bone health.

## 10. Clinical Trials

Presentation by Jeffrey Hyams, MD.

### 10.1. Background

To date, there have been just a small number of prospective trials of therapeutic interventions in children with IBD. The first well-designed, placebo-controlled, adequately powered successful trial of a medication to treat pediatric IBD was published in 2000. It demonstrated the utility of early administration of 6-mercaptopurine in reducing cumulative corticosteroid dosing for children who were newly diagnosed with moderate to severe Crohn's disease. This study took 10 years to complete and was a testament to the endurance of the primary investigators.

Other studies have been published that have been either open-label in design or inadequately powered. The largest pediatric study, completed recently, involved 112 patients. This open-label study, initiated by industry, examined the utility of infliximab in moderate to severe Crohn's disease. It demonstrated the efficacy of a 3-dose induction regimen of 5 mg/kg infliximab in inducing response and remission (at 10 weeks) and showed that

infusions administered every 8 weeks were superior to those given every 12 weeks in maintaining response and remission at 1 year.

### 10.2. Obstacles to Success

There are multiple reasons for the paucity of adequately powered, placebo-controlled clinical trials in pediatric IBD, including the following:

- Infrastructure for pediatric IBD clinical trials has been lacking.
- There has been a lack of funded time for investigators to construct and supervise physician-generated clinical trials.
- Industry has been reluctant to include pediatric patients in phase 2 and early phase 3 trials.
- Communications involving leaders in pediatric IBD research, whether interacting between themselves or with industry, have been suboptimal.
- There has been a lack of optimal communication and planning between organizations in advancing clinical trials research in pediatric IBD.
- There has been inadequate patient education concerning the importance of clinical trials. This stands in stark contrast with what happens in childhood cancer, when the patient on chemotherapy knows that he/she is part of an ongoing protocol and all the data are being stored at a central site. This has not happened with therapies for IBD.

### 10.3. Recommendations for Moving Forward

To address the above issues and to promote important pediatric clinical research initiatives, several recommendations can be made:

- Establish a multicenter pediatric IBD clinical trials steering committee and network sponsored jointly by CCFA and NASPGHAN. The steering committee will act as a contact point for all industry-sponsored pediatric IBD research, ensuring quality control and protection of the rights of patients and investigators. The committee also will assist individual investigators in developing multicenter collaborations when necessary. Data ownership will rest with the investigators, and all projects will be registered before they begin.
- Develop reasonable criteria for pediatric centers to be included in a pediatric IBD clinical trials consortium. For example, centers that wish to participate may need to have a dedicated research nurse/coordinator, adequate numbers of patients, and so forth.
- Obtain more grant funds to support peer-reviewed, high-quality clinical trials research on physician-initiated projects.
- When possible, coordinate with existing infrastructure that supports clinical trials research in adults, and give pediatric investigators the opportunity to sit on leadership panels of the clinical trial steering committee for adults with IBD.
- Interact more with NIH to raise the visibility of pediatric clinical trials.

- Develop educational programs for pediatric patients and their families to increase awareness and acceptability of basic research and clinical trials.
- Standardize pediatric end points and indexes used to define response, remission, and normal growth in children with ulcerative colitis and Crohn's disease.
- Foster collaborations with geneticists, microbiologists, and immunologists to ensure that clinical trials not only assess the efficacy of an intervention but also provide insights and understanding into the pathogenesis of IBD.

#### 10.4. Research Questions

After discussing numerous clinical situations of importance to children and adolescents with IBD, this focus group concentrated on the following areas:

- Prevention of postoperative recurrence following segmental resection in cases of Crohn's disease.
- Better initial therapy for moderate to severe ulcerative colitis to decrease the high rate of corticosteroid dependency and the likelihood of colectomy in this population.
- Better therapies to maintain remission in ulcerative colitis following induction of remission.
- Better strategies to improve growth in children with Crohn's disease who commonly present with impaired growth velocity and in whom postdiagnosis growth velocity continues to be significantly impaired.
- Developing and defining the role of noninvasive surrogate markers to predict preclinical disease activity or postoperative recurrence.

#### 10.5. Issues discussed

The Cystic Fibrosis Foundation has set up a Therapeutic Development Network, which is involved in almost continuous testing of new drugs, new agents, and old drugs with new approaches in partnership with both industry and the NIH. It is hugely effective and allows drug companies to get high-quality centers to perform research.

The formation of a consortium or group would be valuable for several reasons: Pharmaceutical companies need sufficient numbers of patients to conduct even small-scale safety trials, and the consortium would give investigators more control over what is being presented to the pediatric population.

What form would the consortium take? It appears that every area such as genetics, pharmacology, and epidemiology would benefit from a network. Should there be 1 large, creative network with subsets for each field of specialized studies?

Industry may not be interested in conducting true trials in pediatrics unless mandated by the federal government. CCFA and NASPGHAN could help present the case for clinical trials in pediatric IBD to Congress and the FDA.

How does one decide when it is wise to invest heavily in a large infrastructure and when it is not? In the case of cancer,

large clinical-trials work groups were set up and based on 2 essential features: There was a steady supply of patients willing to participate in trials, and there was a steady supply of drugs to be tested. Most of the funding has come from the NIH. On the other hand, in the case of rare diseases, we rarely have something that can be tested, so it is more cost-effective to set up the infrastructure as and when needed for each specific study. An example of an intermediate approach is TrialNet, which focuses on research and testing therapies for type I diabetes in children. In the case of IBD, we may need a limited infrastructure.

CCFA established the Clinical Alliance for gastroenterologists treating IBD in adults. That could be a template to use and learn from.

Creating a consortium of clinical investigators in pediatrics makes sense, but we need to figure out specifics about what the group would do once it is formed. It will be important to have a series of meetings bringing clinical investigators together to think about how to apply themselves in leveraging trials for the benefit of children with IBD.

## VI. RESEARCH AGENDA: A SUMMARY

After extensive discussions by the conference participants, the following 5 areas were identified as the top research priorities in pediatric IBD at the current time.

### 1. Growth and Skeletal Health

The effects of IBD on growth and bone accretion are unique to pediatric patients. Specifically, the focus of this initiative is on the effects of inflammation on linear growth and bone metabolism. These areas can be studied concurrently or independently, depending on the research proposal. The following gaps in knowledge need to be addressed:

- Nutrient limitations and utilization in children with IBD: to understand the availability and utilization of nutrients necessary to achieve normal growth, body composition, and progression through puberty.
- Endocrine axes disturbances in children with IBD: to better understand key endocrine abnormalities in children with IBD and to identify the significant determinants of those most at risk. These include the GH/IGF-I axis and gonadal and adrenal steroids.
- IBD treatment effects on growth: to study the efficacy of modalities used to treat IBD in children on growth and body composition, including pharmacological and nutritional therapies.
- Bone cell function in children with IBD: to define changes in bone modeling and remodeling associated with the inflammatory response in IBD in children.
- Interventions to optimize skeletal health: to test the best approaches to optimize bone mass in children with IBD so that they can reach their genetically determined peak bone mass.

- Impact of IBD on skeletal health in children and adolescents: To understand the natural history of bone mass accrual and bone structure in children with IBD and to differentiate between decreased bone accrual and increased bone loss.

## 2. Genetics

One of the most pressing issues in IBD genetics is the deficiency of knowledge regarding susceptibility genes for early-onset disease and pathophysiological mechanisms that distinguish pediatric-onset IBD from adult-onset disease. Children with a younger age of onset of Crohn's disease and ulcerative colitis are more likely to have a family history of IBD than those of older age of onset. Compared with adult-onset, childhood-onset disease may have greater susceptibility to gene dosage, leading to earlier presentation. Furthermore, childhood-onset IBD is more likely to be based on genetics, with very little time for environmental modifiers (such as smoking) to act. Very little effort has been dedicated to identifying susceptibility genes in exclusively pediatric-onset IBD. The first design issue in studying a complex disorder like IBD is to identify and characterize the right population. Rather than work with convenient samples, this proposal is to study incident cases (inception cohorts) of newly diagnosed, pediatric-onset IBD cases, with prospective characterization of phenotypes. The knowledge gained from genetic studies would not only advance the science of IBD pathogenesis but also elevate the clinical care of IBD in both children and adults.

Two research actions are proposed:

- a) Identify the susceptibility and modifier alleles associated with early age of onset (before age 12) of Crohn's disease and ulcerative colitis using the whole-genome association approach. (For this purpose, it would be useful to work with the Illumina or Affymetrix microarray platform that allows the genotyping of 500,000 SNPs in each experiment.)
- b) Perform genotype-phenotype correlation studies and gene-environment interaction studies of prospectively identified, well-characterized IBD patients in a large, exclusively pediatric-onset IBD cohort.

## 3. Quality Improvement

Health services research suggests that health care could perform a great deal better than it does today. An audit of medical records of a large sample of adults in 12 US cities showed that only 55% of recommended care was being received by patients. Preliminary data indicate that there also is considerable variation in pediatric IBD care. Variation in care can be associated with underuse, overuse, or misuse of available treatments and can lead to lower quality of care, increased cost, and increased morbidity. Quality improvement can reduce variation in care and can improve health outcomes

and QOL. To improve the quality of care of children with newly diagnosed Crohn's disease, 2 studies are proposed:

- a) To conduct a variation in care study with a prospective cohort. It will identify underuse, overuse, and misuse of diagnostic and therapeutic interventions and will identify gaps between recommended and actual care so that the gaps can be closed.
- b) To form an Improvement Collaborative to improve nutrition and growth. It will perform continuous quality improvement to improve the detection, treatment, and prevention of growth delay and growth failure in children with Crohn's disease. The effectiveness of the Improvement Collaborative will be evaluated by a prospective, randomized study with a comparison group (either by randomization or case-control) in which the results of sites completing the Improvement Collaborative can be compared with those from other sites performing care as usual.

## 4. Immunology

The chronic intestinal inflammation in patients with IBD is associated with abnormalities of the mucosal immune response. In light of this knowledge, an in-depth evaluation of the immune response in pediatric IBD is essential to improve our understanding of disease mechanisms in this age group. This will eventually lead to new therapeutic approaches designed specifically for children suffering from Crohn's disease and ulcerative colitis. To achieve these goals, it is essential to understand how IBD evolves from the early to the late phases of disease and how these 2 phases differ in terms of the underlying cellular and molecular mechanisms of inflammation. This proposal is to study changes from early onset and later onset pediatric IBD in the following areas:

- Innate and adaptive immunity.
- Developmental aspects of mucosal immunity.
- Target antigens of the immune response.
- Effects of therapy on the immune response and immune function.

## 5. Psychosocial Issues and Development

Children and adolescents with IBD have higher rates of depression and anxiety than youth with other physical illnesses and normal peers, but there has been little focus on psychosocial issues or their treatment in prepubertal children with IBD. Psychosocial difficulties in the areas of family conflict, peer-related socializing, medical adherence, and absences from school and extracurricular activities also have been reported. These problems further diminish the patients' QOL, even as they deal with a difficult disease course and complicated treatment regimens. A few studies have begun elucidating risk factors for the development of emotional and behavioral

problems, including biological factors (such as depression induced by inflammation-related cytokines or exogenous steroids) and environmental factors (such as poor social support and parental depression). There is, however, a clear need for greater focus on the elucidation of both risk and protective factors and their relationship to the severity and course of IBD to help prevent psychological suffering and to improve overall functioning of the patients. In addition, some studies have investigated the treatment of depression in adolescents with IBD, but there is a need to develop interventions that focus on preventing and treating other psychological aspects such as anxiety, HRQOL chronic pain, and environmental contributors. Two research actions are proposed:

- Identify risk and protective factors regarding depression, anxiety, and related psychosocial difficulties in both children and adolescents with IBD. These studies could include a focus on both biological and social factors to better understand the interactions that involve the brain, gut, immune system, and environmental influences.
- Conduct randomized treatment and prevention studies to reduce emotional suffering (such as anxiety and depression) and to improve global functioning. There is a particular need for specific focus on such areas as medical outcome, medical adherence, social competence, and quality-of-life issues.

## VII. RESOURCE: SETTING UP A NETWORK

The conference participants generally agreed that there is a need to set up a pediatric IBD collaborative network that would serve as a resource for studies by scientists and clinicians in the field. The network would be designed to help answer specific questions, including those raised at this meeting, and other issues that will develop over time.

The network would consist of a single overriding structure encompassing several sections. The sections would focus on supporting different types of studies such as clinical trials; translational research, including research on genetics, immunology, and the effects of inflammation on growth and bone health; and quality improvement studies.

The study of psychosocial issues could potentially be incorporated into the clinical trials subsection.

It was pointed out that the overall network will function more smoothly if it has some form of central governance such as a steering committee, perhaps with a group of advisors. Discussions will be needed to determine how that committee should be formed by holding elections, by selecting individuals and rotating them, or in some other way.

The formation of sections would be sensitive to the fact that different types of studies require different collaborative structures. For instance, translational research requires a setup that differs from that needed for clinical trials or quality improvement research.

Formation of this large network will take time, and the initiation of this process does not need to await the writing of proposals for specific studies. Rather, both need to be done in tandem. It will be important to identify some strong, testable questions, to bring together several centers interested in participating, and to build the infrastructure for data collection and distribution.

It was recognized that several regional consortia have already been set up and are working on various projects. They need to be reassured that this larger network will not be taking away from those projects but will add to them and will facilitate better communication and collaboration between groups.

One advantage of having a network is that it would provide researchers with access to multiple patient resources. An investigator at 1 center may have a great idea for an experiment in translational research but may not have enough patients or resources. Other centers may have many patients but may not have scientists who want to do the research. A network would bring them together, allowing them to share their resources and enabling the project to move forward.

A second advantage is that a unified network would be more successful in raising funds for particular projects by all components. If the network (or section) submits a proposal for achieving 1 or 2 initial goals, along with a longer-term vision for future participation by others, that type of proposal is more likely to receive the backing of potential funding sources. Once the network has resources, it should allocate them to participating investigators and institutions on the basis of the amount of work they do or product they contribute.

Funding for setting up and operating the network needs to be discussed. One suggestion was that CCFA could provide part of the funds, in partnership with the NIH, NASPGHAN, and other organizations. In addition, each institution that participates in the network could make a commitment to supply part of the funds.

The first few projects should be relatively simple and focused, aiming for early success, rather than being broad and all encompassing. Discussions are needed on the issue of whether the initial project should be translational research before a clinical trial or whether it should integrate both types of studies.

Efforts need to be made to foster the interests of junior investigators and to assist them in their development. Such efforts would include funding their fellowships, mentoring them, and giving them authorship and recognition for their work.

Although CCFA has certain resources that are already on-line or are being placed on-line, suggestions would be welcomed on how to expand these resources and form better partnerships with the NIH and other organizations to better serve the needs of those involved in pediatric IBD research and treatment. The common goals would be to find the best practices and best processes, ultimately leading to the best services to the patient community.

### VIII. APPENDIX: MEMBERS OF THE STEERING COMMITTEE

Athos Bousvaros, MD, MPH, chair, Children's Hospital Boston and Harvard Medical School, Boston, Mass.

Robert N. Baldassano, MD, University of Pennsylvania School of Medicine and the Children's Hospital of Philadelphia, Philadelphia.

John A. Barnard, MD, Ohio State University and Columbus Children's Hospital, Columbus.

Richard S. Blumberg, MD, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass.

Jonathan Braun, MD, PhD, David Geffen School of Medicine at the University of California, Los Angeles, and the Jonsson Comprehensive Cancer Center, Los Angeles.

Marla C. Dubinsky, MD, Cedars-Sinai Medical Center and the David Geffen School of Medicine at the University of California, Los Angeles.

Charles O. Elson, MD, University of Alabama, Birmingham.

Barbara S. Kirschner, MD, University of Chicago, Chicago, Ill.

Maria Oliva-Hemker, MD, Johns Hopkins Children's Center and Johns Hopkins University School of Medicine, Baltimore, Md.

D. Brent Polk, MD, Vanderbilt University School of Medicine, Nashville, Tenn.

Stephan R. Targan, MD, Cedars-Sinai Medical Center and the David Geffen School of Medicine at the University of California, Los Angeles.

### IX. MEMBERS OF THE FOCUS GROUPS

#### 1. Genetics

Subra Kugathasan, MD, chair, Medical College of Wisconsin, Milwaukee.

Richard Duerr, MD, University of Pittsburgh, Pittsburgh, Pa.

Anne Griffiths, MD, FRCPC, Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada.

Stephen L. Guthery, MD, Primary Children's Hospital, Salt Lake City, Utah.

Jack Satsangi, MD, University of Edinburgh, Edinburgh, United Kingdom.

Mark Silverberg, MD, PhD, FRCPC, Mount Sinai Hospital, Toronto, Ontario, Canada.

Vasundhara K. Tolia, MD, Children's Hospital of Michigan, Wayne State University School of Medicine, Detroit, Mich.

#### 2. Psychosocial Issues and Development

Eva Szigethy, MD, PhD, chair, Children's Hospital of Pittsburgh/University of Pittsburgh Medical Center, Pittsburgh, Pa.

Ronald Dahl, MD, University of Pittsburgh Medical Center, Pittsburgh, Pa.

Sonia Friedman, MD, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass.

David Keljo, MD, Children's Hospital of Pittsburgh, Pittsburgh, Pa.

Laura Mackner, PhD, Columbus Children's Hospital/Ohio State University, Columbus.

Marci Reiss, MSW, Cedars-Sinai Medical Center, Los Angeles, Calif.

Joel Rosh, MD, New Jersey Medical School, Morristown.

#### 3. Epidemiology

George D. Ferry, MD, chair, Baylor College of Medicine, Houston, Texas.

Devendra K. Amre, MBBS, PhD, University of Montreal and Sainte-Justine Hospital, Montreal, Quebec, Canada.

Anders Ekblom, MD, PhD, Karolinska Institute, Karolinska University Hospital, Stockholm, Sweden.

Benjamin D. Gold, MD, Emory University School of Medicine, Atlanta, Ga.

Antonio Quiros, MD, University of California Davis Medical Center, Davis.

Ernest G. Seidman, MD, FRCPC, FACG, McGill University Health Center and Sainte-Justine Hospital, Montreal, Quebec, Canada.

#### 4. Microbiology

Steven J. Czinn, MD, chair, University of Maryland, Department of Pediatrics, Baltimore.

Charles O. Elson, MD, University of Alabama, Birmingham.

Benjamin D. Gold, MD, Emory University School of Medicine, Atlanta, Ga.

Nita Salzman, MD, PhD, Medical College of Wisconsin, Milwaukee, Wis.

David Schauer, PhD, Massachusetts Institute of Technology, Cambridge.

Ernest G. Seidman, MD, FRCPC, FACG, McGill University Health Center and Sainte-Justine Hospital, Montreal, Quebec, Canada.

Judy B. Splawski, MD, Rainbow Babies and Children's Hospital and Case Western Reserve University, Cleveland, Ohio.

Phillip I. Tarr, MD, Washington University School of Medicine, St Louis, Mo.

#### 5. Immune Response

Claudio Fiocchi, MD, chair, The Cleveland Clinic, Cleveland, Ohio.

Rebecca Adkins, PhD, University of Miami, Coral Gables, Fla.

Salvatore Cucchiara, MD, University of Rome, Rome, Italy.

Ivan Fuss, MD, National Institute of Allergies and Infectious Diseases, National Institutes of Health, Bethesda, Md.

Subra Kugathasan, MD, Medical College of Wisconsin, Milwaukee, Wis.

Simon Murch, MD, University of Warwick, Coventry, United Kingdom.

Theresa T. Pizarro, PhD, University of Virginia, Charlottesville.

David Ziring, MD, University of California Los Angeles, Los Angeles.

## 6. Quality Improvement and Safety

Richard B. Colletti, MD, chair, University of Vermont, Burlington.

Robert N. Baldassano, MD, University of Pennsylvania, School of Medicine and the Children's Hospital of Philadelphia, Philadelphia.

David E. Milov, Nemours Children's Clinics, Orlando, Fla.

Peter A. Margolis, MD, PhD, University of North Carolina, Chapel Hill.

Jonathan E. Markowitz, MD, University of Pennsylvania School of Medicine and the Children's Hospital of Philadelphia, Philadelphia.

Paul V. Miles, MD, American Board of Pediatrics, Chapel Hill, NC.

Robert S. Sandler, MD, MPH, University of North Carolina, Chapel Hill.

Harland S. Winter, MD, Massachusetts General Hospital, Boston.

## 7. Pharmacogenomics

William A. Faubion, Jr, MD, chair, Mayo Clinic, Rochester, Minn.

Carmen Cuffari, MD, Johns Hopkins School of Medicine, Baltimore, Md.

Laurence Egan, MD, National University of Ireland, Galway.

Richard Farrell, MD, James Connolly Memorial Hospital, Blanchardstown, Dublin, Ireland.

Daan Hommes, MD, Academic Medical Center, Meibergdreef, Amsterdam, The Netherlands.

Liewei Wang, MD, PhD, Mayo Clinic, Rochester, Minn.

## 8. Nutrition

Anthony Otley, MD, MSc, FRCPC, chair, IWK Health Centre, Dalhousie University, Halifax, Nova Scotia, Canada.

Andrew S. Day, MB, ChB, MD, FRACP, Sydney Children's Hospital, Randwick, and School of Women's and Children's Health, University of New South Wales, Sydney, Australia.

John Fell, MD, MRCP, FRCPCH, Chelsea and Westminster Hospital, London, United Kingdom.

Anne Griffiths, MD, FRCPC, Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada.

Leslie M. Higuchi, MD, MPH, Children's Hospital Boston and Harvard Medical School, Boston, Mass.

Heidi J. Kalkwarf, PhD, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio.

Babette Zemel, PhD, University of Pennsylvania School of Medicine and the Children's Hospital of Philadelphia, Philadelphia.

## 9. Growth and Skeletal Health

Francisco Sylvester, MD, chair, University of Connecticut School of Medicine and Connecticut Children's Medical Center, Hartford.

Ernesto Canalis, MD, University of Connecticut School of Medicine and Saint Francis Hospital and Medical Center, Hartford.

Catherine M. Gordon, MD, MS, Children's Hospital Boston, Boston, Mass.

Dana S. Hardin, MD, University of Texas Southwestern Medical School and Children's Medical Center, Dallas, Texas.

Mary B. Leonard, MD, MSCE, University of Pennsylvania School of Medicine and the Children's Hospital of Philadelphia, Philadelphia.

Kimberly O'Brien, PhD, Johns Hopkins Bloomberg School of Public Health, Baltimore, Md.

Babette Zemel, PhD, University of Pennsylvania School of Medicine and the Children's Hospital of Philadelphia, Philadelphia.

## 10. Clinical Trials

Jeffrey S. Hyams, MD, chair, Connecticut Children's Medical Center, Hartford, and the University of Connecticut School of Medicine, Farmington.

Robert N. Baldassano, MD, University of Pennsylvania, School of Medicine and the Children's Hospital of Philadelphia, Philadelphia.

Wallace Crandall, MD, Columbus Children's Hospital, Columbus, Ohio.

Anne Griffiths, MD, FRCPC, Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada.

Petar Mamula, MD, University of Pennsylvania School of Medicine and the Children's Hospital of Philadelphia, Philadelphia.

James Markowitz, MD, Schneider Children's Hospital North Shore and New York University School of Medicine, Manhasset.

## X. ACKNOWLEDGMENTS

Challenges in Pediatric IBD was a collaborative effort that depended on the tremendous commitment and dedication of numerous people who participated in this endeavor.

Special thanks go to Dr Athos Bousvaros, chair of the Pediatric Affairs Committee (2002–2005), for his far-reaching vision and leadership; the focus group chairs and participants for their outstanding efforts and extremely valuable input; Drs Marla Dubinsky and Barbara Kirschner for coordinating the conference proceedings; Drs Richard Blumberg, Jonathan Braun, Charles Elson, Stephan Targan, Allan Walker, Wayne Lencer, David Piccoli, and Richard Grand for their input during the meeting; Drs John Barnard (NASPGHAN) and Stephen James and Patricia Robuck from the National Institute for Diabetes and Digestive and Kidney Diseases (NIDDK) for their collaboration and support of this effort;

CCFA lay volunteers Joel Cutler, Mark Goldman, Eugene Kestenbaum, Lisa Richardson, and Suzanne Rosenthal for their enthusiastic support of pediatric research; Dinshaw Dadachanji, PhD, and Margaret Crane, medical writers, for their expertise in preparing the manuscript; Kiren Annigeri, research project coordinator, and Cathy Butler, meeting planner, for their assistance in coordinating the conference in Boston; and Marjorie Merrick, vice president of research and scientific programs, for her overall management of this Challenges initiative.

Dr. Bousvaro was supported in part by the Wolpov family fund and the William C. Ward family fund.