Best Pharmaceuticals for Children Act
Scientific Prioritization Meeting
June 30 and July 1, 2008
Fishers Lane Conference Center
Rockville, MD

This meeting was sponsored by the Obstetric and Pediatric Pharmacology Branch (OPPB), Center for Research for Mothers and Children (CRMC), *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH), U.S. Department of Health and Human Services (HHS) in support of the Best Pharmaceuticals for Children Act (BPCA) Program.

Welcome and Summary of BPCA Legislation

Donald R. Mattison, M.D., Captain, U.S. Public Health Service; Senior Advisor to the Directors of NICHD and CRMC; Chief, OPPB, CRMC, NICHD, NIH, HHS

Dr. Mattison welcomed the participants and briefly summarized the history of BPCA. Over the past 5 years, the success of BPCA has depended on advice and guidance from government institutes and centers (ICs), academia, industry, advocacy groups, and practitioners.

The original BPCA asked NICHD to evaluate off-patent drugs for use in children and to conduct research that contributes to labeling. Since 2002, NICHD has identified drugs and implemented studies in response to that mandate. Advice from expert meetings encouraged NICHD to take a step back from off-patent drugs and labeling and look more broadly at pediatric conditions.

In the 2007 BPCA, Congress shifted the focus from drugs to pediatric conditions. The new legislation encourages NICHD to investigate biologics and devices in addition to drugs. Off-patent drugs and labeling are still an important part of BPCA, and trials begun under the 2002 BPCA will continue.

Goals for the Meeting

Perdita Taylor-Zapata, M.D., Medical Officer, Chair of BPCA Working Group, OPPB, CRMC, NICHD, NIH, HHS

The goals for the meeting are to discuss:
- Summary of BPCA legislation 2002 and 2007
- Transition to new BPCA implementation
- Review of therapeutic areas
- Future directions.

The desired outcome of the meeting is to develop the 2008 priority list of needs in pediatric therapeutics.

Transition to New BPCA Implementation

Pediatric Pharmacology and BPCA: Review of Challenges and Accomplishments

George Giacoia, M.D., Project Officer, Pediatric Pharmacology Research Unit, OPPB, CRMC, NICHD, NIH, HHS
Anne Zajicek, M.D., Pharm.D., Deputy Branch Chief, OPPB, CRMC, NICHD, NIH, HHS

Dr. Giacoia described the evolution of BPCA and challenges in pediatric pharmacology. At the first prioritization meeting in 2002, experts developed an evidence-based list of drugs to study. The current listing process is more sophisticated, and the scope has expanded to therapeutic areas.

Challenges for pediatric pharmacology include:
- Clinical trials
- Biomarkers
- Extrapolation of adult studies to children
- Pediatric formulations
- Gaps in knowledge in key areas of pediatric drug development
- Determination and characterization of adverse drug reactions
- Study of drugs in special pediatric subpopulations
- Role of pharmacogenomics.

Particular problems in designing pediatric clinical trails include determining the appropriate dose, selecting meaningful outcome measures, and analyzing small samples. These factors make it difficult to establish safety and efficacy. Of pediatric drug trials conducted under BPCA, 52 percent were failed trials. Other problems with pediatric trials include a lack of pharmacodynamic (PD) measurements, failure to recognize the need for research, and ethical constraints.

The protocol development team needs to be multidisciplinary, and pediatric pharmacologists should play an integral role. Pharmacometric approaches are an important component of pediatric drug studies.

The 1994 Pediatric Rule states that if the course of a disease, pathophysiology, and effect of a drug or product are sufficiently similar in children and adults, pediatric efficacy can be extrapolated from adequate and well-controlled adult studies. This rule opened the door for studies that might not otherwise have been done, but these assumptions should be critically reviewed.

Diseases have different processes and expressions in children and adults. Phenotype, environment, and other variables can affect disease processes and response to therapy.

A significant number of on- and off-patent drug formulations are not suitable for children, and economic factors are a major impediment to the development of pediatric formulations. The use

of extemporaneous formulations is unsafe. The "carrot and stick" approach of PREA and BPCA has only been marginally effective in encouraging the development of pediatric formulations.

Alternatives to oral liquid formulations are needed, and there are major gaps in knowledge of taste testing and taste blocking for young children. Taste is a major factor in medication noncompliance.

There has been an explosion in the use of biomarkers in the early stages of drug development and in the clinical setting. Biomarkers may be linked to development and may have different expression in children and adults. In clinical trials, biomarkers can help diagnose and characterize disease, establish disease progression and pharmacokinetics (PK) and PD, and measure endpoints and toxicity. Research is needed to establish criteria for validating biomarkers and establishing levels of surrogacy. The use of molecular imaging in pediatric research has lagged behind adult research.

Adverse drug reactions are a problem in pediatric research because of the small number of subjects in pediatric trials, lack of phenotypic characterization of reactions, polypharmacy, and failure to recognize or track adverse drug reactions in children. Databases that track adverse drug reactions are not sufficiently harmonized or integrated. Pharmacoepidemiologic pediatric studies can include larger numbers of patients and longer observation periods than regular randomized control trials.

Issues in developmental pharmacology include a lack of investigators, multidisciplinary teams, and complementary research. There are currently many gaps in developmental pharmacology research, such as a lack of information about genetic variation in drug response and the ontogeny of drug targets. A number of papers have recently linked single nucleotide polymorphisms to susceptibility to disease, but only a handful of these studies have been confirmed. More pediatric pharmacogenomic research is needed.

Dr. Zajicek described the accomplishments of BPCA. The 2002 BPCA included the following considerations for prioritizing drugs:

- Availability of safety and efficacy data
- Need for additional data
- Potential public health benefits
- Need for reformulations.

In the 2002 legislation, the definition of "off-patent" was unclear.

The 2007 BPCA:

- Clarified the definition of "off-patent" as a drug that has no listed patents or has one or more listed patents that have expired
- Calls for a list of priority areas in pediatric therapeutics
- Requires consideration of available information, therapeutic gaps, potential health benefits, and adequacy of infrastructure for research

- Allows NIH to submit a Proposed Pediatric Study Request (PPSR) to the Food and Drug Administration (FDA) as a draft Written Request (WR).

NIH was charged with developing a priority list of pediatric therapeutic areas in consultations with NIH ICs, federal agencies such as FDA and the Centers for Disease Control and Prevention (CDC), pediatric experts and groups, and committees of the American Academy of Pediatrics (AAP). Based on the priority list, FDA submits WRs to holders of new drug applications. If industry declines the WR, it is referred to NIH. Under the 2002 BPCA, NIH issued contracts for research. The 2007 legislation allows funding via contracts, grants, and cooperative agreements.

The FDA has issued WRs for the following drugs since BPCA was enacted:

- Lorazepam
  - Sedation
  - Status epilepticus
- Nitroprusside
- Azithromycin
  - Ureaplasma pneumonia
  - Chlamydia
- Baclofen
- Lithium
- Lindane
- Rifampin
  - Methicillin-resistant *Staphylococcus aureus* (MRSA) endocarditis
  - Central nervous system shunt infections
- Meropenem
- Vincristine
- Dactinomycin
- Ampicillin
- Griseofulvin
- Methotrexate
- Daunomycin

Industry declined the WRs for all of these drugs except lindane. Industry also declined WRs to study the following on-patent drugs (baclofen and metoclopramide changed status from off-patent to on-patent):

- Morphine
- Bupropion
- Sevelamer
- Zonisamide
- Hydroxyurea
- Baclofen
- Dexrazoxane
- Metoclopramide
- Eletriptan

Under BPCA, NIH awarded Premier Research Group the data coordinating center contract and awarded contracts for the following ongoing clinical studies:

- Lorazepam: sedation
  - PK, safety, efficacy
  - Recruitment halted, interim analysis ongoing
- Lorazepam: status epilepticus
  - Study 1: PK, complete and the clinical study report is being prepared
  - Study 2: Efficacy and safety study comparing lorazepam to diazepam, enrolling
- Nitroprusside: reducing blood pressure during surgery to reduce blood loss
  - Study 1 is complete and data monitoring is ongoing
  - Study 2 starts summer 2008
- Lithium: defining treatment of mania in children with bipolar disorder
  - Study 1 has completed enrollment
  - Study 2 starts summer 2008
- Baclofen: treating spasticity, most commonly from cerebral palsy
  - Chart review complete

  - PK/PD study to begin enrollment in July 2008
- Meropenem: treating serious intra-abdominal infections in infants
  - PK/safety study started June 19, 2008
- Hydroxyurea to treat very young children with sickle cell disease
  - National Heart, Lung, and Blood Institute (NHLBI) study
  - Study recruitment complete and 2-year follow-up ongoing
- Vincristine: evaluating neurotoxicity, PK in children (National Cancer Institute [NCI]-Children's Oncology Group [COG])
- Actinomycin-D: evaluating hepatotoxicity/veno-occlusive disease, PK in children (NCI-COG)
  - Study 1: data extraction of National Wilms Tumor Study database for toxicity
  - Study 2: catheter-clearing experiments
  - Study 3: PK modeling of published vincristine, actinomycin-D data to design prospective PK study
  - Study 4: Prospective PK study
- Methotrexate: evaluating neurocognitive outcomes of pediatric patients with high-risk acute lymphoblastic leukemia (NCI-COG)
- Daunomycin: PK, safety, efficacy of daunomycin to treat childhood cancers and relationship to body weight (NCI-COG).

Other projects include:
- Ketamine: preclinical studies to evaluate the scientific and safety concerns
- Methylphenidate: preclinical and clinical evaluation of PK and safety to understand reports of cytogenetic toxicity (National Institute of Environmental Health Sciences)
- Morphine: evaluations of the developmental and safety issues of treating pain in neonates.

FDA Role in BPCA: Challenges and Accomplishments

Hari Sachs, M.D., Pediatric Medical Officer, Pediatric and Maternal Health Staff, FDA, HHS

General principles of pediatric drug development are based on international guidelines:
- Pediatric drugs should be studied with the same robust level of evidence as adult drugs
- When drugs are developed, the effects on children should be studied if there is an anticipated pediatric use
- Pediatric drug development should not delay the availability of drugs for adults.

Comparison of BPCA and the Pediatric Research Equity Act (PREA):

BPCA	PREA
Drugs	Drugs and biologics
Studies voluntary	Studies mandatory
Studies on entire active moiety	Studies only on drug/indication under review
WR may be issued for orphan indications	Studies for orphan indications exempt
Priority review	Standard review (unless qualifying for priority)
Pediatric studies must be labeled	Pediatric studies must be included in label

The 2007 BPCA legislation:

- Reauthorizes FDA Modernization Act exclusivity incentive
- Establishes a new process for studying off-patent drugs
- Requires collaboration between FDA and NIH in development of the priority list of pediatric therapeutics and WRs for off-patent drugs
- Permits NIH to issue a PPSR
- Allows a single WR to include approved and unapproved uses
- Allows a WR to include preclinical studies
- Allows the pediatric review committee (PeRC) to review WRs prior to issuance and to review studies to make recommendations on exclusivity
- Changes timelines so that:
  - All responses to WRs are given priority review
  - Exclusivity determination is made in 180 days instead of 90 days
  - Pediatric exclusivity is only granted if 9 months of exclusivity remain at the time of exclusivity determination, preventing de facto exclusivity
- Requires applicants to submit all available adverse event reports with pediatric study submission
- Requires label to include study information even if the study does not demonstrate safety or efficacy
- Maintains the dispute resolution process between FDA and the sponsor
- Increases transparency by requiring exclusivity determinations to be posted on the Web.

A major change in the 2007 BPCA is that NIH can issue a PPSR. FDA will issue a WR, and industry has 30 days to respond. If the industry accepts, they may get exclusivity. If they decline, the WR is referred to NIH.

Changing the label to include a novel indication for children requires substantial evidence from two adequate and well-controlled trials. All studies must include some assessment of safety, and data monitoring committees may be considered but are not always necessary.

The 2007 PREA requires pediatric study and assessment for new drug applications or supplements with a new active ingredient, indication, dose, or route of administration. Studies may be waived or deferred in certain circumstances. Adequate and well-controlled adult studies can be extrapolated for children, and studies may be extrapolated for different age groups. Pertinent reviews must contain the rationale for extrapolations. The 2007 PREA increases transparency by requiring information about deferrals, formulations not developed, and drug reviews to be posted on the Web.

The 2007 PREA requires pediatric study information to be included in the label, whether the studies demonstrate safety or efficacy or not. If an indication is granted, the information can be incorporated throughout the label. If an indication is not granted, the study information is included in the pediatric use section of the label.

The new labeling has been designed to be more accessible. A half- to full-page “highlights” section describes the recent changes and safety information. Other changes reorganize the label to make it easier to find information.

The PeRC is made up of experts from a wide variety of disciplines, including pediatrics, clinical pharmacology, ethics, and statistics. The PeRC provides a high-level review of BPCA and PREA activities. FDA is preparing a number of reports to Congress on BPCA and PREA.

The participants discussed the following issues:
- BPCA allows waiver of two adequate and well-controlled trials for a new indication; PREA does not.
- PREA allows studies without a data safety monitoring board, but NIH does not approve studies without a board.
- FDA is working on a new process for labeling changes that go through NIH and do not involve industry.
- FDA and the European Medicines Agency (EMEA) have begun sharing information about drug development in the United States and the European Union (EU) through monthly teleconferences and the exchange of WRs and pediatric investigational plans.

NIH Role in the Study of Devices Under BPCA

Steven Hirschfeld, M.D., Ph.D., Associate Director for Clinical Research, NICHD, NIH, HHS

Dr. Hirschfeld provided an overview of laws and regulations related to pediatric drug development from the 1970s to the present and discussed the legal foundation for drug regulations. A device is legally defined as a product that is similar to a drug but does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and is not dependent on being metabolized. In regulatory terms, a combination product is a product that includes two classes of products, such as a drug and a device.

The 2007 FDA Amendments Act includes Title III: Pediatric Medical Device Safety and Improvement Act of 2007:
- Section 302 requires
  - Inclusion of relevant pediatric populations in device protocols and marketing applications
  - Annual reports on FDA activities related to pediatric devices
  - Requirements for extrapolation from adults to children and from one pediatric subpopulation to another
- Section 303 defines "pediatric" as age 21 and younger.
- Section 304 requires NIH to
  - Designate a contact point to identify sources of funding for pediatric medical device development
  - Submit a plan for expanding pediatric medical device research and development.

The pediatric device plan (Section 304), developed by NIH, FDA, and the Agency for Health Care Research and Quality (AHRQ), will include:
- Current status of federally funded pediatric medical device research
- Gaps in research
- A research agenda for improving device development and approval and for evaluating safety and efficacy.

The draft NIH pediatric device plan includes:

- A catalog of current NIH-funded device projects
- A listing of funding programs that target either pediatrics or devices
- A description of research infrastructure that would support device development
- A summary of NIH ethical policy related to enrolling children in clinical trials
- Development of a model that would permit private or public–private funding
- Identification of key elements of the transition from early phase studies to marketing development
- Expectations for publicly funded projects to meet scientific and business objectives.

Participants discussed the following issues:

- Whether a product is a drug or a device depends on its intended use. If the chemical product is used as a delivery mechanism for only one drug, it may be considered a drug. If it can be paired with several different drugs, it may be considered a device.
- The pediatric device plan should address issues of intellectual property and profitability of device development.
- Novel devices require clinical trials, but devices that are improvements over existing mechanisms may be licensed without a trial.

Moving from Individual Drug Listing to Needs in Therapeutic Areas: The Prioritization Process

Dr. Taylor-Zapata

NICHD administers BPCA, and 19 ICs contribute funding for this research. Since implementing BPCA in 2002, NICHD has learned numerous lessons about pediatric research:

- There is a lack of preclinical, phase I, and phase II trials.
- Children may have unanticipated adverse drug reactions.
- Drugs may have long-term effects on growth and development.
- Ethics and feasibility are issues in pediatric clinical research.

These lessons highlight the need for increased basic science research, epidemiology research, and novel clinical trial designs. NICHD has sought expert opinion early in the process of studying off-patent drugs and focused requests for proposal on specific types of research. Under BPCA, NICHD has discussed 106 drugs with experts, identified 61 priority drug/indication pairs for pediatric studies, and responded to 80 percent of the WRs it has received. No labels have been changed.

Under the new legislation, NIH is responsible for:

- Studying of off-patent drugs, including drugs that have no exclusivity for at least one form of the drug
- Publishing a priority list of needs in pediatric therapeutics every 3 years
- Considering the availability of information and infrastructure for research
- Funding research with contracts, grants, and other mechanisms
- Submitting PPSRs to the FDA

- Submitting a feasibility study and report to Congress
- Including pediatric pharmacologists in career development and loan repayment programs.

NICHD plans to prioritize therapeutic areas over the next 4 years by:
- Building on the foundation established by the 2002 BPCA
- Evaluating the currently listed drugs and therapeutic areas for new therapeutic gaps and retiring inactive drugs
- Changing the listing process to focus on pediatric therapeutics
- Determining new areas of need in pediatric therapeutics.

The plan for prioritization includes:
- Defining boundaries of therapeutics and therapeutic needs
- Gathering data to identify gaps
- Consulting with experts in pediatric research
- Consulting with FDA to determine gaps in labeling and study design
- Developing priority categories for therapeutic areas and priority scores for drugs.

Each year, NICHD will select a priority category. Priority categories will include diseases of high prevalence, high morbidity and mortality, public health impact, and limited treatment alternatives, as well as rare diseases and diseases and indications within special populations.

NICHD will identify off-patent drugs, biologics, and/or devices through consultation with pediatric experts. Priority scores will be assigned based on the level of evidence, frequency of drug use, severity of the disease, and potential benefit of research.

One or two primary categories have been determined for each year:
- For 2008, conditions with increasing prevalence and/or public health concerns (hypertension, asthma—outpatient care, pediatric infections)
- For 2009, conditions with high health burden/severity (biodefense, asthma—intensive care unit [ICU] care, anesthetic agents)
- For 2010, public health areas/rare diseases (psychiatry, neurology, oncology)
- For 2011, special populations (neonates, adolescents)
- For 2012, conditions with limited alternative therapies available (fragile X syndrome, type-1 diabetes)
- In the future, rheumatology, renal diseases, gastrointestinal diseases, and other infectious diseases.

Discussion

Lead Discussants: Philip Walson, M.D., Cincinnati Children's Hospital Medical Center
Bob Ward, M.D., University of Utah
Jeffery Barrett, Ph.D., Children's Hospital of Philadelphia
Wayne Snodgrass, M.D., Ph.D., University of Texas Medical Branch

Dr. Ward raised the following issues:

- Neonates should be included in therapeutic categories.
- Scientific needs must be matched with resource availability when considering how many studies can be funded under BPCA and for how many years.
- NIH should consider conflicts of interest—both financial conflicts and subspecialty biases
- Industry and the U.S. Pharmacopeia (USP) are underrepresented and should be more involved.
- The priority scoring system should be published.
- FDA has started publishing pediatric guidelines, and NIH could help with this effort.
- FDA is working with industry to develop pediatric trial designs.
- Over-the-counter products should have been included in the prioritization process for BPCA.
- Individual toxicity should be examined.
- Concentration is more important than dose and should be studied.
- It is important to consider how to change behavior in taking medications. AHRQ and USP could help inform this topic.
- Pediatric research should involve more long-term follow-up.
- Infrastructure for pediatric pharmacology research involves nurses and psychologists as well as doctors and pharmacists.

Dr. Barrett made the following comments:

- Adult drug development is focused on gaps, but pediatric drug development is primarily a process of extrapolation.
- Diversity of types of research should be built in early in the research program.
- It would be beneficial to examine the diversity of pediatric prescribing practices and link practices to outcomes. It is important to understand differences between practices and labeling.
- Parents would be a good source of feedback.

Dr. Snodgrass raised the following issues:

- The AAP Committee on Drugs is revising its pediatric research statement, and participants are encouraged to submit comments on the topic of data monitoring boards to the committee.
- Not enough pediatricians are trained to conduct research in clinical pharmacology.
- Devices are increasingly needed for the site-specific delivery of drugs.
- Pediatric drug concentration cannot always be extrapolated from adult data. Concentration may change with development.
- Research on therapeutic needs in developing countries, such as malaria, HIV, and tuberculosis, should be encouraged.
- Drug companies and pediatricians should be more directly involved in pediatric drug development.

Open Discussion. The participants discussed the following issues:

- NICHD should be a clear leader in the study of ontogeny and conduct research on how human development affects diseases and therapies.
- FDA is developing side effect profiles based on data in electronic medical records (EMRs). Pediatric populations need to be part of this effort.
- Dosing information for children should be part of computerized physician order entry systems.
- A review process should be carefully considered if industry will be involved as a partner in pediatric drug development.
- Evidence-based information needs to be translated to the practitioner community.
- Age-based and weight-based subpopulations have been considered in pediatric dosing. Other characteristics, such as gender, body composition, physical activity, and race and ethnicity, should be considered in dosing and incorporated into trial design.
- Drugs may have unknown reactions when taken with herbals and nutraceuticals.
- The long-term risks of giving children drugs during certain developmental periods should be acknowledged.
- Studies need longer follow-up to assess long-term outcomes and the duration of adverse drug reactions. At the same time, the desire for long-term follow-up should not paralyze research that can examine more practical, short-term outcomes.
- Concerns about long-term outcomes are raised by studies of neonatal drug exposures that do not have adequate prospective randomization.
- NICHD needs to provide more clarity about the resources available to implement BPCA.
- It is important to consider whether drug indications are based on diseases or on surrogate markers. In some cases, drugs are used to treat markers when the diseases and outcome targets are not well understood.
- Pediatric data need to be incorporated into the development of drugs for asthma and infections.
- Children have been excluded from research on biomarkers and genetic screening, and they should be included.
- To allocate resources more effectively, NICHD should plan research in smaller increments so that initial outcomes can inform next steps.
- NICHD should use practice-based research networks to conduct studies, disseminate information, and provide long-term follow up. However, there are ethical issues involved when physicians recruit their own patients for research.
- Assembling research groups for each project is inefficient. Pediatric pharmacology research would benefit from the development of a durable research network similar to COG.
- Regulatory decisions cannot be based on published literature for which the source documents and audit trails are not available.
- For most drugs, the portion of the label on breast milk is left blank.
- More research on the developmental aspects of prescription drug abuse is needed.
- Some of the issues raised during this session could be addressed by other NICHD initiatives or by the National Children's Study rather than BPCA.
- The EU has pediatric research networks and requires adult drug applications to include pediatric investigation plans. Unless pediatric drug research in the United States becomes

better organized, the EU is likely to drive the process in the future. FDA and EMEA regulations need to be harmonized.

Review of Therapeutic Areas Being Pursued 2008–2009

Review of Pharmacoepidemiology Analyses

James Korelitz, Ph.D., Associate Director and Senior Epidemiologist, Westat
Norma Gavin, Ph.D., Senior Fellow in Maternal and Child Health, RTI International

Dr. Korelitz explained that epidemiology involves:
- Descriptive of analytical studies
- Observational or experimental study designs
- Primary or secondary data sources.

Pharmacoepidemiology frequently, but not always, relies on secondary data sources such as:
- Vital statistics (birth, death records)
- Medical/health studies or surveys
- Insurance claims data
- EMRs.

Each data source has strengths and limitations, depending on the features of the data source:
- Cross-sectional versus longitudinal data
- Definition of cohort/denominator
- Patient/parent-reported versus physician-recorded data
- Size and representativeness of population and subgroups
- Other nuances of how data are collected/recorded.

Recommendations. To prioritize pediatric therapeutic areas for further study, relevant questions might be:
- What percentage of youths receives a particular medication?
- Among youths with a particular diagnosis, which medications have they received?
- Among youths given a particular medication, what diagnoses did they have?

Westat prepared prevalence reports based on secondary data from commercial insurance, Medicaid, and medical and hospital records. Instead of only examining one medication and condition at a time, these secondary data sources can be used to study concomitant medications and comorbidities.

Results from pharmacoepidemiologic analyses can be combined with literature reviews of previous studies (clinical and epidemiology) and expert opinion to identify gaps in knowledge.

Participants discussed the following issues:
- More drugs are prescribed to Medicaid patients because there is a higher burden of illness in those patients.

- It is difficult to identify neonates in some databases; children younger than 1 year old are identified as age 1 in the Medicaid database.
- Not all databases include weight.
- Children covered by Medicaid do not have access to the full range of available medications.

Dr. Gavin presented the results of a pharmacoepidemiologic study of trends in blood pressure measurements among children 2–17 years old based on a nationwide sample of EMRs from 2000 to 2006. The database was used to answer numerous questions about blood pressure in children and to discover several trends in pediatric blood pressure and the diagnosis and treatment of hypertension in children. However, complete and accurate record keeping must be maintained for these data sources to achieve their maximum benefit.

Recommendations. Further analysis is needed to determine:
- Why substantial differences exist between the EMR estimates and estimates from prospective population-based studies.
- Whether the apparent underestimation of hypertension diagnoses in EMR databases are real and the reasons for the discrepancy.

Respiratory Diseases (Asthma) Therapeutic Needs

Primary Reviewer: Thomas Green, M.D., Children's Memorial Hospital
Discussants: Alan Stiles, M.D., North Carolina Children's Hospital
Jeffrey Blumer, M.D., Ph.D., Case Western Reserve University

Asthma is a research priority because it is a leading cause of childhood disease and a significant burden on children and their families. The prevalence of childhood asthma doubled between 1980 and the mid 1990s, and the causes of asthma are not well understood. There are significant racial disparities in the prevalence of asthma.

Key differences between the 1997 and 2002 expert panel reports on asthma:
- The critical role of inflammation has been further substantiated, but evidence is emerging for considerable variability in the pattern of inflammation, thus indicating phenotypic differences that may influence treatment responses.
- Gene-by-environmental interactions are important to the development and expression of asthma. Of the environmental factors, allergic reactions remain important. Evidence suggests a key and expanding role for viral respiratory infections in these processes.
- The onset of asthma for most patients begins early in life with the pattern of disease persistence determined by early childhood. Recognizable risk factors including atopic disease, recurrent wheezing, and a parental history of asthma.
- Current asthma treatment with anti-inflammatory therapy does not appear to prevent progression of the underlying disease.

The four components of asthma management are:
- Measures of assessment and monitoring—obtained by objective tests, physical examination, patient history and patient report—to diagnose and assess the characteristics and severity of asthma and to monitor whether asthma control is achieved and maintained

- Education for a partnership in asthma care
- Control of environmental factors and comorbid conditions that affect asthma
- Pharmacologic therapy.

Gaps in current knowledge about asthma include early diagnosis and intervention, prevention of progression, management of severe asthma, and improved management of severe exacerbations.

NHLBI, the National Institute of Allergy and Infectious Diseases (NIAID), and NICHD have research networks studying pediatric asthma.

Recommendations. Additional needs for asthma research include:
- Validating an objective, reproducible, widely applicable method to measure airway obstruction and reactivity in children younger than 6 years old
- Performing comparative studies of drug delivery systems for children younger than 6 years old
  - Inhaled corticosteroids
  - Short-acting beta agonists
- Performing randomized, controlled, efficacy trial of addition of long-acting beta agonists to inhaled corticosteroids in children younger than 4 years old with moderate, persistent asthma that is not well controlled
- Deferring ICU-based trials pending completion of prospective epidemiologic studies of current therapies.

Dr. Stiles discussed the following issues:
- Research on reactive airway disease is needed.
- Research should be driven by pediatric and adult allergists.
- Drug measurement and delivery are critical.
- Compliance is an important issue is asthma therapy.

Dr. Blumer suggested that studies investigate why some children do not respond to asthma therapies and whether adherence is a problem.

Infectious Diseases Therapeutic Needs

Primary Reviewer: Theoklis Zaoutis, M.D., M.S.C.E., Children's Hospital of Philadelphia
Secondary Reviewer: Bernhard L. Wiedermann, M.D., Children's National Medical Center

Community-acquired MRSA (CA-MRSA) was first reported in Chicago in 1998, and its prevalence has increased over the past two decades. Unlike hospital-acquired MRSA, CA-MRSA is only resistant to beta-lactam antibiotics. A majority of CA-MRSA infections are skin and soft tissue infections. Incision and drainage may be adequate for treatment of lesions less than 5 centimeters in diameter. Clindamycin, trimethoprim/sulfamethoxazole, and vancomycin can also be used to treat CA-MRSA, but additional research is needed.

Research is needed to determine whether fluoroquinolones are safe for treating arthropathy and tendinopathy in children. Because these are rare conditions, pharmacoepidemiologic studies may be helpful. Formulations and PK of benzathine penicillin G also need more research.

Dr. Weidermann made the following points:
- The differences between CA-MRSA and hospital-acquired MRSA (HA-MRSA) and between MRSA and methicillin-susceptible *Staphylococcus aureus* (MSSA) are blurring.
- Clindamycin resistance has increased from 15 percent to 25 percent, and resistance has increased more in some regions than others.
- Clindamycin has a bad taste, and the formulation affects the viability of the drug.
- Better data and evidence are needed about the rates of emerging infectious diseases.
- Rifampin should be removed from the priority list.
- The adverse events associated with quinolone antibiotics, such as joint pain, are subjective, and a double-blind study is needed. Use of quinolones may drive up pneumococcal resistance.
- In Europe, there is an emphasis on treating neonates.
- Penicillin G benzathine, used to treat rheumatic fever, needs more study.

Psychiatry Diseases Therapeutic Needs

Primary Reviewer: Robert Findling, M.D., University Hospitals Case Medical Center
Discussants: Daniel Safer, M.D., Johns Hopkins University School of Medicine
Margaret Rappley, M.D., Michigan State University

Depression is common in children and adolescents, recurrent/chronic, pernicious, and potentially lethal. Pharmacotherapies for depression include selective serotonin reuptake inhibitors, tricyclics, monoamine oxidase inhibitors, and other new agents.

Bupropion has a unique mechanism of action.

Recommendations. Topics to consider with bupropion:
- Distinct PD and possible clinical implications
- Acute safety and efficacy (suicidality)
- Long-term safety and efficacy
- Use in other disease entities/comorbid conditions with depression.

Dr. Findling discussed the BPCA study of lithium for the treatment of pediatric mania—the Collaborative Lithium Trials (COLT). The objectives of COLT were to:
- Develop evidence-based dosing strategies for lithium in children and adolescents
- Thoroughly characterize the PK/biodisposition of lithium in pediatric patients
- Conduct a randomized, placebo-controlled study examining the acute efficacy of lithium in children and teenagers with mania
- Conduct a randomized trial examining the efficacy of lithium as a maintenance treatment for children and adolescents with bipolar 1 disorder
- Develop a meticulous and comprehensive characterization of the short- and long-term safety of lithium in children and adolescents.

All atypical antipsychotics have distinct PD profiles, and there are individual differences in symptom amelioration and tolerability/side-effect profiles.

Recommendations. Topics to consider for atypical antipsychotics:
- Long-term safety
- Head-to-head comparison studies
- Uses in combination with other agents.

Participants discussed the following issues:
- The focus of the National Institute of Mental Health (NIMH) is shifting from psychopharmacology to brain imaging and genetics.
- Polypharmacy is an issue in treating psychological and behavioral problems.
- Primary care physicians have been encouraged to provide mental health care, and pediatricians need continuing medical education on mental health.

Dr. Safer made the following points:
- Bupropion is not very effective in children.
- Risperdal is increasingly used to treat aggression, and there are concerns about long-term outcomes.
- Rates of autism and bipolar disorder are increasing, and it is important to establish criteria for diagnosis of psychological disorders.

Dr. Rappley agreed that it is important to understand the risks and benefits of Risperdal and bupropion. A major public health issue is that children covered by Medicaid are less likely to be diagnosed with depression but more likely to be treated with atypical antipsychotics.

Hypertension Update: Pediatric Hypertension Clinical Trials

Speaker: Jennifer Li, M.D., Duke University Medical Center
Primary Reviewer: Joseph Flynn, M.D., M.S., Children's Hospital and Regional Medical Center
Discussants: Jonathan Sorof, M.D., AstraZeneca
Thomas Wells, M.D., M.B.A., University of Arkansas for Medical Sciences

Dr. Li discussed a collaboration between FDA and Duke University to study pediatric hypertension that involved data from 11 efficacy and safety studies, 1998–2005, and analyzed trial design, safety, and response.

Most of the clinical trials failed to show a dose response. This could be due to lack of efficacy or an improper dosing range in the study. The trials that were successful had large differences between dosing ranges so there were not overlapping exposures between dose groups. The successful trials also developed liquid formulations. The results showed that the dosage of antihypertensive agents was more closely related to a reduction in diastolic blood pressure than reduction in systolic blood pressure.

Recommendations. Successful trials had several common design components:
- Diastolic blood pressure as the primary endpoint
- Larger difference in dosage between low- and high-dosage groups
- Pediatric formulation used in efficacy trial.

Placebo controls in pediatric hypertension trials are safe, and the placebo withdrawal phase demonstrated blood pressure lowering response despite lack of dose response for most agents.

Future directions for BPCA research include:
- Developing an exposure–response model using adult and pediatric data to perform clinical trial simulations of pediatric studies and explore trial designs and analysis options
- Designing pediatric trials by leveraging previous quantitative knowledge
- Routinely collecting blood samples at informative time points to assess PK in each subject to ascertain exposure response.

Dr. Flynn provided an overview of pediatric hypertension:
- Hypertension in children and adolescents is increasing in prevalence; much of the increase is fueled by the obesity epidemic.
- Hypertension in the young is frequently missed in primary care settings.
- Drug treatment is indicated in a select set of clinical conditions.
- No current guidance exists as to what classes of antihypertensive agents are best for childhood hypertension.
- Current prescribing data indicate that angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, beta blockers, and clonidine are most commonly prescribed.
- Long-acting agents appear to be preferred by prescribers over short-acting agents.

Propranolol and captopril should be considered for study in children age 6 and younger. Dr. Wells recommended that hydrochlorothiazide diuretic be studied.

Dr. Sorof made the following points:
- There is interest in studying the use of beta blockers in children. There is good evidence of a relationship between obesity and sympathetic overdrive.
- Combination therapies should be studied.
- Metatoprol lowered blood pressure but did not reach the endpoint.
- Drugs that already have good pilot data should be studied further.

Biodefense Therapeutic Needs

Speaker: David Siegel, M.D., OPPB, CRMC, NICHD, NIH, HHS
Respondents: J. Routt Reigart, M.D., Medical University of South Carolina
Robert Leggiadro, M.D., Lincoln Medical Center

The Project BioShield Act of 2004 provided HHS with several new authorities to expedite the development and deployment of medical countermeasures against biological, chemical, nuclear, and radiological agents. NIH was given a lead role, and many institutes are involved. NIAID was designated the lead NIH institute and is responsible for studying infectious diseases and

radiation. The National Institute of Neurological Diseases and Stroke (NINDS) is responsible for studying chemical agents.

There are numerous gaps in biodefense therapies for children:
- The military conducted research and development with adult males as study models.
- Because 80 percent of pediatric drugs are off label, they cannot be included in the Strategic National Stockpile (SNS).
- Children were labeled as a "special population," which made them a low priority.
- There are ethical issues with pediatric and obstetric trials.
- Children and pregnant women have lacked a voice in biodefense planning.

The 2007 BPCA provides opportunities to address biodefense gaps for children and pregnant women. Toxic exposures before conception and during pregnancy can affect children. Newborns and children face different risks than adults.

Major issues include:
- Emergency medical services are not prepared to treat children after an attack.
- User-friendly treatment modalities and decontamination units are designed for adults.
- In explosions, children are likely to suffer different injuries than adults.
- Children have a smaller airway, lower blood volume, and different vital signs than adults.
- Correct pediatric dosages are often not known.
- Children are more vulnerable to chemical attack because they inhale a greater dose, absorb more toxin through their skin, and are closer to the ground.
- Nerve agents penetrate the blood-brain barrier more easily in children.
- CHEMPACKS do not include pediatric-dosed autoinjectors for diazepam or pralidoxime chloride, and they do not include intramuscular midazolam because its use is off label.
- Atropine has minimal therapeutic affect in pediatric nerve agent exposure. Scopolamine may be more effective but has not been studied.
- Children are more vulnerable to bioterrorism attacks. Ciprofloxacin and doxycycline are the preferred treatments, but they pose risks to children.

Biodefense working groups have been formed to discuss pediatric issues in countermeasures for infectious diseases, chemical agents, and radiation. The working groups have input into government priorities and the SNS, and they will address how to study countermeasures in children or juvenile animals.

Dr. Reigart recommended the following:
- More information is needed about using scopolamine to treat organophosphate poisoning.
- The majority of children exposed to organophosphates do not have central nervous system effects, although the literature indicates the opposite. It may be easier to study organophosphate poisoning in the developing world than in the United States.
- Other oximes should be evaluated.
- The use of statins as neuroprotectors should be investigated.
- It is important to develop simple countermeasures for first responders.

Review of Therapeutic Areas Under Consideration 2010–2012

Special Populations: Therapeutic Needs in Fragile X Syndrome

Speaker: Tiina Urv, Ph.D., NICHD, NIH, HHS
Responder: Jacob Aranda, M.D., Ph.D., State University of New York Downstate Medical Center

Fragile X syndrome (FXS) is the most common inherited cause of intellectual disability, affecting about 1 in 2,500 people. It produces a wide range of cognitive and behavioral problems and medical problems. Polypharmacy is a major issue in the treatment of symptoms in children with FXS.

FXS is a single-gene disorder. The full FXS mutation leads to silencing of the gene, causing a deficiency in fragile X mental retardation protein (FMRP). The lack of FMRP leads to alterations in protein synthesis throughout the brain, as FMRP appears to be an inhibitor of many translational activities. Metabotropic glutamate receptor subtype 5 (mGluR5) activation initiates protein synthesis, and FMRP suppresses it. Researchers are developing and studying mGluR5 antagonists that may be used to treat FXS.

There are a number of challenges is conducting a trial of FXS therapy. It is a rare disorder, making it difficult to recruit enough subjects. It is a developmental disorder, and trials in adults may not produce measurable results. Cognitive deficits, behavioral problems, and concomitant medications may pose additional problems.

Dr. Aranda shared additional information about FXS. PK data from studies of autism therapies may be extrapolated to FXS patients, but PD, efficacy, and safety may be different in patients with FXS because this disorder affects gamma-aminobutyric acid (GABA) A receptors.

Pharmacological approaches have been identified that may compensate for the loss of FMRP, and therapeutic approaches now need to be developed to improve the quality of life of patients with FXS.

Recommendations. The following issues must be considered in designing clinical trials for FXS therapies:

- The problem of choosing primary outcomes from an array of symptoms
- Polypharmacy
- Combination therapies
- Inclusion and exclusion criteria (for example, whether non-FXS autistic children should be excluded)
- Genetic studies
- Imaging studies
- Age range
- Informed consent.

Type-1 Diabetes Therapeutic Needs

Speaker: Gilman Grave, M.D., NICHD, NIH, HHS
Responder: Stephen Spielberg, M.D., Ph.D., Dartmouth Medical School

Dr. Grave provided an overview of TrialNet—a network of sites in the United States, Canada, and the EU that screens family members of individuals with type-1 diabetes, who have a higher risk of the disease. Among identical twins of individuals with type-1 diabetes, only one-third has the disease. This means that environment plays a role.

Insulin is not a cure for diabetes. Because evidence suggests that type-1 diabetes is immunologically mediated, immunomodulatory therapies may be effective. The goal of TrialNet is to delay or prevent type-1 diabetes by:

- Exploring novel therapies in new-onset cases
- Exploring preventive treatment in relatives of probands and in individuals at high genetic risk
- Further defining epidemiology, natural history, and risk factors.

The following pathways are being evaluated:

- Immunosuppression (mycophenolate mofetil)
- T-cell modulation (anti-CD3, thymoglobulin)
- B-cell modulation (rituximab)
- Costimulation blockade (abatacept)
- Antigen-specific therapy (oral insulin, GAD-Alum)
- Metabolic control (continuous subcutaneous insulin infusion with continuous glucose monitoring)
- Nutritional therapy (omega-3-fatty acid).

TrialNet has undertaken the following studies of interventions in new onset diabetes:

- Studies that have completed enrollment
  - Mycophenolate mofetil with and without daclizumab
  - Rituximab (anti-CD20 antibody)
- Studies that are currently enrolling
  - Abatacept
  - GAD-Alum Vaccine (Diamyd).

TrialNet is studying the following preventative therapies:

- Therapies identified in natural history study
  - Oral insulin
  - Anti-CD3 (teplizumab)
- Therapy for primary prevention in newborns
  - Docosahexaenoic acid.

The potential risks of immunomodulatory interventions need to be examined.

Dr. Spielberg noted that although insulin is not a cure, it has provided significant health benefits over the last 100 years, and significant improvements have been made in insulin and insulin administration. Immunomodulatory treatments target the causes and mechanisms of diabetes, but there are potential challenges and long-term effects of these types of treatments. The immune system is not well understood. NICHD should focus on understanding the developmental aspects of diabetes and the immune system.

Participants discussed the following issues:

- Research is needed to determine whether ACE inhibitors can prevent diabetic neuropathy in children.
- TrialNet is dedicated to prevention and new onset of type-1 diabetes; another network may be needed to look at established treatments.
- The risk of secondary malignancy will be a problem in immunomodulation studies. This issue needs to be adequately covered by consent forms.

Anesthesia Research in BPCA

Speaker: Cheng Wang, Ph.D., FDA, HHS
Discussants: Lynne Maxwell, M.D., University of Pennsylvania
James Chamberlain, M.D., Children's National Medical Center
Sunny Anand, M.B.B.S., D.Phil., University of Arkansas for Medical Sciences

Dr. Wang presented preliminary data and a plan for an *in vivo* study to assess the affects of gaseous anesthetics in the developing nonhuman primate. Anesthesia has been shown to cause widespread and dose-dependent neurotoxicity in developing rodents. Susceptibility is limited to periods of brain growth spurts.

The nonhuman primate study will focus on the commonly used inhaled anesthetics nitrous oxide and isoflurane. The goal of the study is to determine whether nitrous oxide or isoflurane, used alone or in combination, produces exposure time-related increases in neurotoxicity and whether neuronal cell death is primarily apoptotic or necrotic. The study will investigate whether L-carnitine can prevent or attenuate neuronal cell death and behavioral deficits. Long-term pathological changes and the relationship of those changes to long-term behavioral deficits will also be examined.

Preliminary data show no significant effects when rodents were exposed to nitrous oxide or isoflurane alone. The combination of nitrous oxide and isoflurane had no effect after 2 hours. However, after 6 hours, the combination has a neurotoxic effect. L-carnitine at doses of 100 mg/kg or higher was shown to attenuate neurological damage. Neural cell death was primarily apoptotic in the developing rodent.

Phase I of the nonhuman primate study will determine the doses and time course over which nitrous oxide and isoflurane increase neuronal cell death and/or changes gene expression. Phase II will determine the dose-response and time relationships between neurotoxicity and long-term behavioral consequences. Phase III will use advanced imaging techniques to determine whether L-carnitine can protect against neurotoxicity and prevent the associated behavioral changes.

Dr. Maxwell made the following points:

- Physicians used to avoid giving gas anesthetics to neonates, but in the 1980s and 1990s, Dr. Anand and his colleagues demonstrated the harms of untreated pain.
- Most anesthesia studies focus on short-term efficacy and do not examine long-term effects.
- Little is known about how anesthetics work.
- Gas anesthesia administered without ventilation control can affect pulmonary blood flow and carbon dioxide levels.
- Little is known about periods of vulnerability to neurotoxicity.
- It is not known whether emergence delirium or epileptic form changes caused by sevoflurane might be related to pathologic abnormalities in infants.
- There are concerns about drawing parallels between animals and humans because of differences in dose and duration of exposure.
- Children have anesthesia for painful procedures, but studies give anesthesia to animals in the absence of painful stimulus. Pain may alter the effect of anesthetic on the nervous system.
- Studies that could provide information about the effects of anesthesia on children include
  - Analysis of registry information
  - Sibling studies
  - Cognitive testing of children who receive general anesthesia and children who receive regional anesthesia over several years.
- Ketamine protects the nervous system in some situations. Gas anesthesia before cardiac surgery has a protective effect.

Dr. Chamberlain noted that ketamine has revolutionized emergency care in United States. It is short acting, does not have respiratory effects, and is safe in the short term. Apoptosis in rodent models is worrisome, but rodents received 10 times the clinical dose. A ketamine arm should be added to the nonhuman primate study.

Dr. Anand raised several issues:

- Anesthesia studies were conducted in 7-day-old rats, which have the brain maturation equivalent to a 16-week human fetus. The results may be relevant for fetal surgery but may not apply to newborns.
- A rodent study conducted in France showed that morphine in the absence of pain and pain in the absence of morphine cause cognitive effects, but the effects of morphine and pain together canceled each other out.
- Studies by John Olney, M.D., used 140 mg/kg of ketamine, which is 100 times the dose used for human newborns.
- An exposure time of 6 hours in the rodent study is the equivalent of 2 weeks of human development.
- Studies have shown that ketamine is neuroprotective in the presence of inflammatory pain.

Neurology Therapeutic Needs

Discussants: Janice Brunstrom, M.D., Washington University School of Medicine (lead)
George Ricaurte, M.D., Ph.D., Johns Hopkins University School of Medicine

Cerebral palsy is caused by a nonprogressive injury to the developing brain that occurs before birth or at the time of birth. The prevalence of cerebral palsey has been estimated as 2–3/1,000 live births worldwide. A CDC study suggests the prevalence in the United States is higher and is increasing.

The impairments associated with cerebral palsy have not been well investigated. Gaps in cerebral palsy treatment include:

- Lack of consensus in treatment or management for children this disorder
- No understanding of epidemiology
- Lack of understanding of medical issues that complicate cerebral palsy
- Lack of study of those most severely effected.

The BPCA baclofen trial demonstrated that secondary medical problems such as bladder impairments and gastrointestinal problems affect drug therapy. Secondary medical problems also have a profound impact on the quality of life for children with cerebral palsy.

NICHD should study secondary medical issues associated with cerebral palsy in greater depth.

Participants discussed the following issues:

- It is important to distinguish between spasticity and dystonia.
- Improvements in cerebral palsy therapy could serve as a model for the management of other chronic diseases.
- Constipation is a common problem in children with neurological diseases.
- There is no consensus on the pathogenesis of most types of cerebral palsy. Imaging and pharmacogenomic studies may help identify potential therapies.

Special Populations: Therapeutic Needs in Neonates

Discussants: Alan Jobe, M.D., Ph.D., Cincinnati Children's Hospital
John Van Den Anker, M.D., Ph.D., Children's National Medical Center
Sunny Anand, M.B.B.S., D.Phil., University of Arkansas for Medical Sciences

Diseases and therapies are different for term and preterm infants, and a wider range of diseases and conditions affect term infants. Dosing for newborns cannot be extrapolated from dosing for children or adults because PK, PD, and safety issues are very different. Most of the drugs used in the neonatal ICU (NICU) have never been tested in neonates, and efficacy and safety are hard to evaluate. The off-label use of drugs is very common.

Issues for using drugs in newborns include:

- Intravenous drugs are toxic or too concentrated.
- Oral formulations are unsuitable (crushed tablets may release drug too quickly and taste may be an issue with oral solutions).

Dr. Jobe presented a ranked list of the most commonly used drugs in NICUs:
- Antibiotics are the most used drugs in the NICU.
- The most misused drugs are metoclopramide and ranitidine.
- The most commonly used drugs for pain are fentanyl and morphine.

Trends in the use of drugs in the NICU show that education can reduce the use of problematic drugs.

Neonates have had serious adverse reactions to drugs in the past, and history should not repeat itself. Adverse drug reactions are more likely to be recognized in older children than in infants, so assessment is a problem.

Recommendations. Priorities for research might include:
- Proving that certain drugs (like gastrointestinal drugs) do not work in neonates
- Providing evidence for the efficacy and safety of commonly used drugs
- Figuring out how drugs that relieve pain and suffering can be used safely.

Dr. Van Den Anker emphasized that neonatologists and clinical pharmacologists should be involved early in the development of clinical trials.

Future Directions

Open Discussion of Other Areas of Therapeutic Needs

Oncology: Pat Reynolds, M.D., Ph.D., Children's Hospital of Los Angeles
Victor Santana, M.D., St. Jude Children's Research Hospital
Dermatology: Rosalyn Epps, M.D., Children's National Medical Center
Gastroenterology: William Berquist, M.D., Stanford University Medical School
Other Areas: Expert Panelists, Public Comment

Oncology. Dr. Reynolds discussed research on the use of 13-cis retinoic acid to treat neuroblastoma. A COG study with 12 years of follow-up showed an improved survival rate when 13-cis retinoic acid was added to myeloablative therapy. In the phase I study, the PK was variable, and patients were probably underdosed. Effective dosing may improve outcomes. The formulation of 13-cis retinoic acid is not optimal for young children. There are opportunities for studies that would:
- Improve dosing and administration in young children
- Enable labeling changes
- Enhance PK data
- Examine combination therapies for brain tumors.

Most pediatric oncology drugs are off label. Pediatric research on current cancer therapies could improve safety and outcomes.

Dr. Santana proposed studying the use of corticosteroids in the treatment of cancer. Steroids play an important role in the treatment of cancer in children, such as leukemia and lymphoma, but they also produce adverse effects—aggressiveness, myopathies, and avascular necrosis (AVN)—that are not well understood. More research on the prevention and treatment of AVN is needed. Steroids are used to treat other pediatric conditions, so additional research could benefit many areas of pediatric therapeutics. Additional research on the anticancer drug etoposide is needed.

Participants discussed the following issues:

- Dexamethasone is commonly used to treat cancer, but other steroids are used as well.
- Leukemia studies would offer the largest population of patients and long-term survivors.
- Studies could help develop diagnostic methods and early prevention measures for AVN.
- Studies of steroids should examine neurocognitive outcomes.
- BPCA stimulated the development of a pediatric preclinical testing program for pediatric tumors.
- COG has prevented researchers from enrolling pediatric cancer patients in studies of other drugs such as pain medications.

Dermatology. Dr. Epps discussed two priority drugs with dermatological indications: griseofulvin and hydrocortisone valerate. Griseofulvin is used to treat tinea capitis, a common fungal infection of the scalp and hair. The indicated dosing is 10 mg/kg/day for 6–8 weeks, but pediatricians have found that this dose is ineffective and prescribe higher doses. Hydrocortisone valerate is a topical steroid used to treat dermatitis. Age, area of the body, occlusion, and skin condition all affect the absorption of topical steroids. There is a great deal of concern about the impact of topical steroids on height, but it is not known whether the effects are significant or long term.

Dermatitis is a high-prevalence condition with a significant public health impact. Safe and effective pediatric therapies are needed. A BPCA study could (1) determine whether higher doses of griseofulvin are safe and effective and (2) examine the long-term safety of hydrocortisone valerate and effects on growth and hypothalamic-pituitary-adrenal axis suppression. Dermatitis should be a priority pediatric therapeutic area.

Gastroenterology. Many issues in gastroenterology cross over into other subspecialties. Dr. Berquist agreed that the management of gastrointestinal problems in children with cerebral palsy and infants are important issues.

BPCA studies should examine:

- The management of gastroesophageal reflux
- The use of proton pump inhibitors (PPIs) in preterm infants and children younger than 1 year
- Innovative ways to manage cholestasis
- Innovative ways to manage central line infections
- Obesity and fatty liver disease and steatohepatitis
- Crohn's disease and other autoimmune diseases
- Gastric emptying, nausea, and vomiting.

PK studies in children younger than 1 year old would be feasible, especially in the NICU, but it would be difficult to persuade families to participate in PD studies. Basic science research is needed to establish endpoints. The results of PK studies of PPIs in preterm infants and children younger than 1 year old will be published soon.

Open Discussion. The participants raised the following issues:

- Doxycycline and ciprofloxacin are not safe treatments for inhalation anthrax in children. Alternatives such as azithromycin should be considered. The new anthrax vaccine may be safer for children.
- Broselow tape could allow rational dosing adjustments in emergency therapy.
- More study is needed before scopolamine replaces atropine as a treatment for organophosphate exposure.
- More data are needed about hydroxocobalamin, which is used to treat cyanide poisoning.
- Midazolam could be administered nasally or rectally in emergencies.
- Drugs with a number of indications and therapeutic areas should be prioritized.
- Obesity should be a high priority.

Plans for the Coming Year and Summary

Dr. Mattison

When Congress implemented BPCA, it recommended a budget of $200 million per year, but this funding was not allocated. In 2002, the director of NIH gave $5 million to BPCA. In 2003, NICHD provided funding for a coordinating center, and in 2004, contributions from 19 NIH ICs funded BPCA.

NICHD will continue ongoing trials and invest in priority areas such as:

- Hematology and oncology, with new work with retinoic acid
- Diabetes, especially the role of immunomodulators in type-1 diabetes
- Asthma
- FXS, which offers unique opportunities to examine genetic mechanisms of disease
- Psychiatry
- Adolescence
- Cerebral palsy
- Hypertension
- Infectious diseases
- Pain
- Dermatology
- Gastrointestinal disorders
- Crosscutting areas such as
  - Developing pediatric formulations that can be turned into products
  - Safety and efficacy endpoints
  - Understanding of long-term consequences
  - Developmental aspects of disease expression and response to intervention.

NICHD will also:

- Support training for pediatric pharmacologists
- Investigate the feasibility of developing a formulary
- Explore parallels and joint efforts between the United States and the EU and Canada
- Balance limited resources to continue current studies and address emerging needs.

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