Introduction

The meeting was opened by George Giacoia, M.D., from the Obstetric and Pediatric Pharmacology Branch (OPPB) of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, who then introduced Anne Zajicek, Pharm.D., M.D., Branch Chief of the OPPB.

Dr. Zajicek thanked the group for attending and explained that three areas have been selected—asthma, diabetes, and psychiatry—for which to develop connections between clinical pharmacology outcome measures in adults and children. The intent is to identify clinical endpoints and biomarkers for these areas in adults and then determine where they might be applicable for children. Strategies for qualifying and validating these endpoints will need to be determined, including the potential inclusion of original endpoints, secondary outcomes, and ongoing clinical trials or proposed trials. The end goals are to create a collaborative plan for educating fellows in clinical pharmacology, to develop provisional endpoints in pediatric and adult therapeutic trials, and ultimately, to bridge pediatric pharmacology and pediatric subspecialties disciplines and between pediatric and adult clinical pharmacology.

Overview

Dr. Giacoia presented an overview explaining the need to integrate clinical pharmacology and disease-specific therapeutic issues. The Initiative to Advance Pediatric Therapeutics has several purposes, including improving knowledge about pediatric therapeutics, enabling pediatric drug development, and better understanding the role of development and process in relation to disease expression and biodisposition/effects. It is often assumed that development and process exist on a continuum, but they instead follow different temporary patterns related to various factors. Disease processes in pediatrics may be different from those in adults and can include complex multifactorial diseases with various phenotypes. There is a need to look at the interaction between disease and environment in children and the influence of other variables, and to remember that knowledge of natural history is sometimes limited.
Pediatric diseases do not always get progressively worse, and pediatric patterns may be unique or substantially different from those in adults. In order to advance the field, pharmacometricians and pharmacologists need to communicate with subspecialists and work collaboratively to increase knowledge. More studies are needed on pediatric populations, including newborns and preterm infants, pediatric intensive care patients, children with “super orphan” diseases or chronic diseases, adolescents, and children with concomitant diseases/conditions.

Special challenges of this initiative are related to the fact that most development trials have been conducted in adults, so there remains a need for validated measures of endpoint assessments for pediatrics. It is of utmost importance that researchers determine if and when endpoints or outcome measures change at certain ages. Currently, there is a huge lack of knowledge about the ontogeny of drug targets and very limited data about biomarkers. More direct and focused approaches are needed, particularly related to pathways.

The initiative’s working groups were asked to determine the high-level issues for their respective area and to develop justifications for the research that is needed to optimize pediatric therapeutics. Representatives from each working group were invited to present a brief overview of their area during the meeting.

Jeffrey Blumer, M.D., Ph.D., noted that the goals for this meeting were to provide an update about the therapeutic issues, discuss areas where biomarkers may exist or may be needed to advance the understanding of therapeutics, and determine where there are opportunities to engage in training in these areas.

**Asthma**

Stanley Szefler, M.D., presented the issues and justifications developed by the Asthma Working Group.

**Pathophysiology Issues**

**Issue 1:** A need for longitudinal data to determine the changes that occur in the underlying pathophysiology of asthma over the course of a lifetime and its impact on clinical manifestations and prognosis.

**Justification:** Although asthma can present in adults, its origins begin in childhood. One of the difficulties of studying the pathophysiology of asthma is that clearly it differs between adults and children, particularly children younger than age 6. Preschool children have intermittent patterns of disease that are primarily triggered by viral respiratory infections.
**Issue 2:** The need to better understand the relationship between the severity of asthma and the inflammatory response.

**Justification:** The magnitude of airflow limitation and air trapping in children ages 6 to 12 is significantly less than in adults, and it seems to correlate to structural changes as the disease progresses. The airflow obstruction typically is episodic in nature and reverses either spontaneously or with medications.

**Issue 3:** The need for improved measures to determine lung function in children younger than age 6.

**Justification:** Although most adults with asthma typically have a progressive loss of lung function over time, lung function is maintained in a relatively normal range in the vast majority of children outside of exacerbations. Children ages 5 and older can reliably perform spirometry, but lung function measurements in preschool aged children are difficult to obtain.

**Issue 4:** A need for an improved method for assessing inflammation across the ages.

**Justification:** Most data related to underlying airway inflammatory responses are derived from studies conducted in older children and adults.

**Genetics of Asthma and Asthma Pharmacogenetics**

**Issue 5:** There are only limited studies surrounding this area, and the majority of the research has been conducted on adults in general populations of European White descent.

**Justification:** Considerable variability exists in the clinical response to asthma medications in both adults and pediatric populations. Studies are needed about genes that are known to regulate pharmacokinetics in order to tease out gene-function relationships that are relevant to asthma pharmacology.

**Diagnostics**

**Issue 6:** A lack of objective diagnostic tools for young children, particularly in relation to disease management and natural history of disease.

**Justifications:** First, a paucity of data exists about young children to determine transient viral-induced wheezing versus more chronic, persistent wheezing that becomes established asthma. Second, better diagnostic and objective tools are needed for asthma and asthma management. In particular, it is difficult for young children to implement and properly perform spirometry and lung function examinations. Third, longitudinal follow-up is needed to determine the natural history of asthma and what predicts ongoing severe persistent asthma.

**Issue 7:** No true biomarkers exist that fit all criteria in the field of asthma. It is considered a clinical syndrome, and the diagnosis and management are based largely on symptoms. A true biomarker must meet the following criteria:

- Distinguishes the “normal” from asthma
- Changes with exacerbation and normalizes with treatment
- Is stable over time and consistent across the age spectrum.

**Justification:** More large studies are needed in children to investigate whether a biomarker can predict response to therapy or natural history of the disease.

**Outcome Measures**

**Issue 8:** Clinical trials are not necessarily the same for adults and children. At this point, no attempts have been made to standardize asthma outcomes across the spectrum of pediatric asthma trials. Pediatric-specific outcomes are needed for asthma clinical trials so as to better assess pharmacologic efficacy and safety.

**Justification:** There are important differences in asthma physiology, etiology/natural history, and diagnosis across the age spectrum. Therefore, it is not appropriate to extrapolate asthma outcomes from adult studies to the pediatric population, and separate outcomes are needed for infants and preschoolers, prepubertal children, and adolescents.

**Natural History**

**Issue 9:** A need to develop new strategies for the prevention of asthma.

**Justification:** Asthma inception often occurs during preschool years and can have lifelong consequences, and current strategies are ineffective in preventing asthma.

**Issue 10:** The need to develop new strategies to prevent viral-wheezing and asthma exacerbations.

**Justification:** Asthma exacerbations are more common in children than adults, and current therapies are only partially effective at preventing them.

**Issue 11:** A need to develop a greater understanding of between gender differences in relation to the inception, persistence, and remittance of asthma, and how gender relates to therapy responses.

**Justification:** Gender is an important factor in the natural history of asthma: boys outnumber girls in the first decade of life, and women outnumber men and tend to have more severe disease; the switch appears to occur during puberty, but the underlying factors are poorly understood.

**Issue 12:** The need to identify which children will develop progressive loss of lung function over time and why.

**Justification:** Lung function is relatively maintained in the majority of children, but progressive loss of lung function occurs in a subset of individuals. This has had a significant impact on morbidity associated with asthma as children progress through the teen years into adulthood. Identifying who develops asthma and why could lead to disease-modifying strategies. The evolution of asthma in some patient populations may result in chronic obstructive pulmonary disease (COPD), which would be an important relationship to understand.
Pharmacology of Existing Therapeutic Agents

**Issue 13:** Inhaled steroids are commonly used in children younger than age 5, which is outside the age range of scientific evidence and U.S. Food and Drug Administration approval. They are usually delivered to children through metered dose devices with spacers, but little information is known about the impact of drug delivery to the lungs. There are concerns about the potential for systemic absorption and incidence of adverse effects, and there is limited evidence of efficacy in children, particularly in assessing lung function.

**Justification:** In children younger than age 5, there is a need for pharmacokinetic studies comparing nebulizers with MDI/spacer delivery to assess response, systemic absorption, and efficacy. Improved outcome measures relevant to this age group are needed, particularly related to the understanding of pulmonary function testing.

**Issue 14:** (1) Intravenous (IV) beta agonists are commonly used in pediatric intensive care units for severe refractory asthma; (2) there are important gaps in clinical pharmacology of beta agonists in the pediatric population, and efficacy is uncertain; (3) there is variability in clinical applications in relationship to dose and medication; (4) there are unknown dose-related risks of cardiovascular side effects; and (5) there is a lack of appropriate pediatric formulations.

**Justification:** The following are needs: appropriate trials related to age-appropriate formulations, asthma assessment tools related to age and disease severity, age-related pharmacokinetics and pharmacodynamics of IV terbutaline, and age-related efficacy and safety of IV terbutaline.

**Issue 15:** No therapy exists for disease modification or prevention in children. Omalizumab is the only IgE-blocker approved for children older than age 12 who have IgE-triggered environmental antigen sensitivity. Although experimental data suggest that use of omalizumab in early childhood may prevent or modify the course of asthma, it has the potential for serious adverse effects, including delayed anaphylaxis and malignancies, so these risks need to be evaluated.

**Justification:** Controlled clinical trials are needed in children younger than age 5 to evaluate safety, long-term effects, and efficacy. Also needed are successful studies around validating the asthma predictive index, physiologic pulmonary function testing, and age-appropriate immunologic testing.

Dr. Szefler explained that many members of the Asthma Working Group are also members of the National Heart, Lung, and Blood Institute’s (NHLBI’s) AsthmaNet, and they are currently developing a cross-age protocol. This task will help focus the group’s attention on addressing cross-age issues. Dr. Szefler thanked Dr. Giacoia and the NICHD for the opportunity to discuss and summarize this information for future development of asthma medications in children.
Audience Questions. A question was asked about bone density and the intention to evaluate long-term growth in children treated with inhaled steroids. Dr. Szefler responded that these topics were implicit in the discussion about inhaled steroids and the adverse effects and systemic absorption. The most comprehensive study to date that looks at inhaled steroids and persistent asthma was with the NHLBI Childhood Asthma Management Program. It assessed children over 5 years of treatment; children were then followed into early adulthood. It found that within the first year of treatment there was a 1-centimeter delay in growth that appears to be persistent, but not progressive. This delay occurred with a low-to-medium dose of inhaled steroids. There is no information regarding use of high-dose inhaled steroids, and most of the formulations have only been studied for about 1 year in duration of treatment, so information is limited. One study assessed bone density and showed no significant impact on density. Studies about other steroids, other doses, and in the absence and presence of spacers are lacking.

A question was asked about pharmacogenetics related to asthma therapy. Dr. Szefler said the NHLBI Asthma Clinical Research Network focused on this and that there does seem to be some pharmacogenetic specificity in terms of duration of effect with short-acting beta agonists. However, it does not appear to hold up with long-acting agonists. In addition, there are some genetic markers related to steroid response that have been published in the past year in the New England Journal of Medicine. There is a need to take those genetic markers identified through retrospective analysis and do prospective studies. The NHLBI AsthmaNet network is formulating studies to address this issue and to determine whether individuals with identified genetic markers demonstrate a similar response in a prospective study to validate their utilization and clinical management.

It was noted that in terms of adverse effects of high-dose inhaled steroids, cortisol suppression is not unusual. Perhaps the asthma group could work with endocrinologists to help to determine whether patients on steroids have ACTH cortisol measurements during therapy, how to handle suppression of the hypothalamic-pituitary-adrenal axis, and what asthma specialists should be looking for. Dr. Szefler said cortisol is a good biomarker of systemic effect, but there is debate about which one to use in experiments. For example, 24-hour urinary free cortisol, overnight plasma cortisol, overnight urine cortisol, or morning plasma cortisol can be used. The working group will be dealing with this issue when studying steroid response.

A question was raised about special groups that may need extra attention. Premature infants need particular attention because they are the highest users of some of these drugs and there is no knowledge of their pharmacology. Some Neonatal Intensive Care Unit Network follow-up databases could be extended into older age groups to find therapeutics for this group.
Diabetes

William V. Tamborlane, M.D., presented the issues determined by the Diabetes Working Group. He first noted that the basic pathophysiology for type 1 and type 2 diabetes is quite similar between adult and pediatric populations, and the differences between the two groups are more quantitative than qualitative. For type 1, the origin for both adults and children is autoimmune destruction of beta cells, but the destruction is accelerated in young children. With type 2 diabetes, patients in both adults and pediatric populations are characterized by obesity, severe insulin resistance, and progressive β-cell dysfunction. The difference between the populations is that obesity and insulin resistance are relatively greater contributors to alterations in glucose metabolism in pediatric patients, while β-cell dysfunction is a greater contributor in adults.

Identification of new diagnostic biomarkers to differentiate between type 1 and type 2 would be useful, because the only tests currently available are measurements of autoantibodies against elements in the beta cells that indicate the autoimmune process of type 1 diabetes. The most important biomarker that assesses control of diabetes is the hemoglobin A1c (A1C) test, which measures average blood glucose level over the past 3 months. The Diabetes Control and Complications Trial (DCCT) showed that lowering A1C levels to near-normal values can prevent or delay the microvascular complications of diabetes. Thus, A1C tests serve as a surrogate biomarker of the efficacy of diabetes treatments in terms of preventing diabetes complications. Dr. Tamborlane presented some of the key issues and justifications determined by the working group.

**Issue 1:** The need for better diagnostic tests to differentiate type 1 from type 2 diabetes in obese adolescents.

**Justification:** The differentiation between type 1 and type 2 diabetes in obese adolescents is difficult to assess. This is because obesity does not protect against and may actually accelerate the development of type 1 diabetes, and the presence of obesity blurs differences between the two types of diabetes in clinical presentation and metabolic alterations at time of diagnosis. Current diagnostic biomarkers are far from optimal, as determinations of seropositivity to islet antigens are negative in up to 15 percent of patients with type 1; conversely, seropositivity to one islet antigen can be seen in patients with type 2.

**Issue 2:** Would obese adolescents with type 1 diabetes benefit from treatment with metformin or other anti-diabetic agents in addition to insulin?

**Justification:** Obesity in youth with type 1 diabetes is now very common, and it leads to insulin resistance and increased insulin requirements and contributes to greater glucose variability and additional weight gain. Societal trends in obesity and better control of diabetes have resulted in average body mass index z-scores in children and adolescents with type 1 diabetes that are 0.6 to 0.7 standard deviations above the mean. There is a need to determine whether metformin, which enhances insulin sensitivity and is associated with weight loss, could benefit children with type 1 diabetes.
**Issue 3:** Should seropositive teenagers with the clinical features of type 2 diabetes be treated with insulin?

*Justification:* Adults with type 2 diabetes who have seropositivity to islet antigens have more aggressive disease, higher A1C levels, and lesser responses to oral hypoglycemic agents than seronegative adults with type 2 diabetes.

**Issue 4:** The need for better and more robust biomarkers to identify children who are at very high risk for the development of type 1 diabetes.

*Justification:* This issue is of importance because many of the therapies being proposed for prevention of type 1 diabetes have unacceptably high risks for individuals who will not go on to develop the disease, and current methods are not specific enough to exclude such individuals. Moreover, current methods used to identify individuals at high risk for the development of type 1 diabetes are not conducive to mass screening.

**Issue 5:** There is a need for better predictive biomarkers of those who will respond to immunotherapies designed to stem the decline in c-peptide in children with established type 1 diabetes, as well as pre-type 1 diabetes. Current β-cell preservation studies are directed at patients who already have type 1 diabetes and still have 15 to 20 percent of their β-cell population, and there are major gaps in knowledge on how these immune interventions actually change the immune system and lead to type 1 diabetes.

*Justification:* Accurate predictors of responders would allow tailoring of therapies to those children most likely to benefit from them.

**Issue 6:** The need for better prognostic biomarkers of future complications of type 1 diabetes.

*Justification:* Susceptibility to vascular complications appears to have a genetic component. However, there are no specific predictors of which children are at highest risk of developing the long-term vascular complications of type 1.

**Issue 7:** Should children and adolescents with new-onset type 1 diabetes or high-risk pre-type 1 diabetes be eligible for inclusion in β-cell preservation studies, particularly as there could be risk of adverse side effects?

*Justification:* β-cell destruction appears to occur at an accelerated pace in youth with type 1 diabetes when compared with adults. Thus, pediatric patients may be the best group in whom to demonstrate the efficacy of drugs targeting β-cell destruction.

**Issue 8:** Should new drugs for the treatment of type 2 diabetes in pediatric populations be tested against placebo as an add-on therapy in patients with elevated A1C levels on metformin alone; namely, metformin + new drug versus metformin + placebo?

*Justification:* Mandated study design issues have impeded approval of drugs for the treatment of youth with type 2 diabetes. Many past studies required subjects to be drug naïve and have elevated A1C levels. The new drug was to be tested against metformin as monotherapy. However, metformin is well established as initial monotherapy of type 2
diabetes, and almost all youth with the disease who have elevated A1C levels are already being treated with it. Thus, it is difficult to find patients who meet the study inclusion and exclusion criteria.

**Issue 9:** Although A1C levels are almost always the primary outcome measure of efficacy of treatment diabetes, other efficacy outcomes need to be established, especially for patients who are well controlled on current therapy.

**Justification:** Although use of continuous A1C glucose monitoring devices to measure hypo- and hyperglycemic exposure and glucose variability is promising, better measures of the impact of treatment on living with diabetes are needed.

**Issue 10:** Methods and biomarkers are needed to assess the long-term safety of drugs being tested for use in the treatment of type 2 diabetes in pediatric populations.

**Justification:** Long-term cardiovascular and other safety studies are being mandated for the approval of new drugs for treatment of type 2 diabetes in adults. However, the methods to assess potential adverse effects of such treatments in young people with type 2 diabetes have not been established.

**Audience Questions.** It was asked whether or not anyone has looked at osteocalcin levels as a biomarker. Dr. Tamborlane responded that he was not aware of the use of osteocalcin as a biomarker in diabetes.

**PK/PD**

Eda Cengiz, M.D., and Michael Spigarelli, M.D., Ph.D., presented a brief discussion about pharmacokinetics (PK) and pharmacodynamics (PD). They discussed the PK/PD of insulin in pediatric patients, along with challenges and potential solutions.

PK is what the body does to boluses of insulin determined by changes in plasma insulin levels over time. PD is what boluses of insulin do to the body, and that is most accurately determined by glucose infusion rates (GIR) during euglycemic clamp studies. Euglycemic clamp studies are the accepted gold standard test to assess in vivo effect of injected insulin. The rate of glucose infusion required to maintain constant glycemia provides a measure for the net effect of insulin on whole body glucose metabolism.

Children are not small adults, and adolescents are neither bigger children nor smaller adults. Insulin action differs by group, even with the same preparation. The unknowns are: (1) the effect of diluted doses; (2) the effect of puberty and hormones; and (3) the effect of adiposity, obesity, and nutrition. Another challenge is that assays of insulin analogs vary, and there is a need to develop new measures to demonstrate insulin action. It is also important to identify subgroups in the population that show differential responses to insulin treatment.
In relation to adiposity/obesity, the role of insulin resistance in type 1 diabetes needs to be studied, along with the increased weight gain that is associated with insulin treatment. In terms of treatment of adolescents with diabetes, there is a need to study body composition changes (hormonal changes), changing insulin requirements, adherence issues, and insulin action across puberty. There is also a need to develop ultra-fast acting insulins, methods to accelerate insulin action, new long-acting insulin analogs, smart insulins, and different routes of insulin administration.

**Pediatric Psychiatry (Mood Disorders)**

Robert Findling, M.D., M.B.A., presented the issues developed by the Psychiatry Working Group. He noted that mood disorders are common and chronic in young people and are serious, even potentially lethal (due to suicide). There is a need to look at the underpinnings of failed studies in order to develop new and improved therapeutics for children. Also needed is a better understanding of the pathophysiology of mood disorders to develop new and improved therapeutics for children. Because relationships between exposure and response are not generally present for psychotropic therapeutics, child psychiatry depends on extrapolating from adult exposures in order to draw comparisons and find potential modifications from adult dosages.

Psychiatry treats clusters of syndromes, and diagnosis is based on syndromatic criteria. Underpinnings of mood disorders are not just biological, as environment has a clear influence on them and chronic stress and life events can affect the function of the central nervous system. Substantial progress has been made in the field of child psychiatry, but there is still much more to learn.

There is a need to find measures more sensitive to change. In relation to manifestations of mood disorders, the field is not yet ready for translational medicine such as biomarkers to fully enter routine clinical care. Identifying pathology versus developmentally expected norms is challenging, but only through translational medicine will psychiatry progress to the level it needs to reach. The field needs to better understand the pathophysiological underpinnings through translational research while still moving forward with current knowledge.

Mood disorders are recurring chronic conditions frequently associated with bad long-term outcomes and not much is known about their determinants. It is still unknown what starts or stops these conditions. The major risk factors for these conditions are genetic, yet babies are not born clinically depressed or suffering from episodic mood disorders. There is a need to discover what triggers the onset the episodic events and what stops them. Eighty percent of children with major depressive illness never receive treatment, yet sometimes their episodes dissipate, and then recur. Researchers need to determine what is turning on the episodes as one means by which to find long-term approaches to treatment.
Only recently have agents been approved by the U.S. Food and Drug Administration for pediatric mood disorders—two for major depressive illness and four for treatment of mania. The group will continue working on the issues Dr. Findling presented, will solicit more input, and will ultimately include attention deficit hyperactivity disorder (ADHD) as an area of study.

**Audience Questions.** It was asked whether there are thoughts about how to partner with colleagues and look at some of the related mechanisms within areas such as diabetes and psychiatry. Dr. Findling noted that funding and budgets for this work may be an issue, but that there are connections between type 2 diabetes and psychiatric issues. There is also a possible connection between type 1 diabetes and depression that has an organic, autoimmune component.

It was asked whether there is any progress in using MRIs and neurotransmitters as biomarkers in pediatric psychiatry. The short answer is “yes.” Although these approaches are being studied, they are not yet ready for routine clinical use.

**Conclusion**

Dr. Giacoia closed the meeting by talking about next steps. There will continue to be promotion of interaction, collaboration, and partnerships with academia, industry, other federal agencies, and existing consortiums. An inventory of current initiatives, programs, and research in therapeutic areas is needed, and as biomarkers are a major issue, these will be addressed in a systematic fashion. He also noted that for better inclusion of pediatrics, group members need to advocate for a research line extending adult studies of predictive biomarkers of drug toxicity and organ-specific drug toxicity.

Dr. Giacoia explained that other groups, such as neurology and infectious diseases, may be added. In addition, webinars may be used to obtain external feedback about the core groups’ recommendations.

Dr. Giacoia thanked the group for attending and closed the meeting.

**Participant List**

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