

Pediatric Hypertension Treatment Working Group Meeting
April 7, 2006
Marriott Bethesda North Hotel and Conference Center
North Bethesda, MD

This meeting was sponsored by the Obstetric and Pediatric Pharmacology Branch (OPPB), Center for Research for Mothers and Children (CRMC), National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH), U.S. Department of Health and Human Services (DHHS).

Welcome

Donald R. Mattison, M.D., Chief, OPPB, CMRC, NICHD, NIH, DHHS, and Perdita Taylor-Zapata, M.D., Pediatric Medical Officer, OPPB, CMRC, NICHD, NIH, DHHS

Dr. Taylor-Zapata welcomed meeting attendees and thanked them for their participation. She noted (1) that the treatment of pediatric hypertension is an important topic in the field of pediatric pharmacology and (2) that this second meeting of the Pediatric Hypertension Treatment Working Group will continue to identify gaps in scientific knowledge and determine key research agendas and treatment approaches for pediatric hypertension.

After thanking attendees for their participation and hard work to date, Dr. Mattison reported that Best Pharmaceuticals for Children Act (BPCA) annual process to develop a list of off-patent drugs has become very efficient in identifying drugs that need further dosing, efficacy, and safety information. The program staff has been conducting continuous internal reviews of its pediatric drug prioritization process and has determined that it may not have been as effective in identifying key conditions and treatments in pediatric medicine that need further research. In an effort to maximize the gathering of sufficient data and to target key areas of research interest in the medical community, OPPB is moving from the previous individual drug/indication model to a therapeutic class or condition-based model.

Improving the treatment of pediatric hypertension provides an opportunity for NICHD to enhance public health through research and translation into best practices. Although BPCA has been implemented primarily by OPPB, partners in this effort include all NIH institutes and centers that are involved with hypertension research and treatment. Under BPCA, one of the first steps for improving pediatric hypertension treatment was to gather preliminary condition-based data, including:

- Mortality, hospitalization, and physician visits for hypertension among children aged birth to 17 years
- Number of children with a dispensed medication and drug prevalence for antihypertensive drugs for children aged birth to 17 years—Medicaid population, 2000
- Number of children with a dispensed medication and drug prevalence for antihypertensive drugs for children aged birth to 17 years—Commercial/health maintenance organization population, 2004.

These preliminary reports were prepared by two OPPB contractors (Westat and RTI International). Other information, such as a list of oral antihypertensives studied for pediatric exclusivity, was prepared by the Food and Drug Administration (FDA). In addition, the National Heart, Lung, and Blood Institute issued in February 2005 a document titled Short Version of Long-term Plan for Research and Translation in Hypertension for Enhancing Public Health.

In concluding, Dr. Mattison asked the attendees to suggest how OPPB can improve the data it is gathering for BPCA and to identify areas that need to be examined in further detail. In fulfilling its new BPCA goal of improving drug by condition, and to make the discussions more rationale, the OPPB staff is open to comments, questions, or suggestions for additional searches in its databases.

Introductions, BPCA Overview, and Workshop Goals

Dr. Taylor-Zapata

After the meeting participants introduced themselves, Dr. Taylor-Zapata briefly reviewed BPCA, with an emphasis on listing process activities and accomplishments for 2002–2005. She described the listing process approach for 2006 and beyond, the potential role of experts in the BPCA listing process, and the goals of the 2005 and 2006 Pediatric Hypertension Treatment Working Group meeting goals.

Dr. Taylor-Zapata provided background information on the priority list of off-patent drugs:

- BPCA, which was signed into law in January 2002, directs the Secretary of the DHHS, acting through the Director of the NIH and in consultation with the Commissioner of the FDA and experts in pediatrics and pediatric research, to develop and prioritize a list of off-patent drugs for which pediatric studies are needed.
- NIH institutes' and centers' liaisons have participated actively in compiling the priority list of off-patent drugs required by BPCA. NICHD, in consultation with liaisons from other institutes and FDA, developed a prioritization process over the past 4 years to select approximately 15 candidate drugs on an annual basis for consideration for study from the list of approximately 180 off-patent drugs.
- In previous years, drugs for priority study were selected from a master list of off-patent drugs provided by FDA. In addition, the program staff conducted mass outreach mailing to pediatric organizations to obtain information on the use of these drugs in children.
- Of the total drugs discussed and reviewed to date, 47 drugs, with 51 indications, have been listed as off-patent priority drugs that require further pediatric studies.

Dr. Taylor-Zapata characterized the new listing process approach for 2006:

- This year, NICHD and FDA begin their fifth cycle of the annual process to develop a list of off-patent drugs prioritized for study under the provisions of BPCA. During the past year, the program staff conducted internal reviews of current practices in prioritizing drugs for study in children.
- In an effort to maximize the potential of gathering sufficient data and targeting key areas of research interest in the medical community, the program staff is considering modifying its

past practice of an individual drug/indication approach to a therapeutic or condition-based approach.

- With this condition-based approach, the goal is to determine key research agendas in key areas of pediatric medicine, such as attention deficit/hyperactivity disorder (ADHD), asthma, infectious diseases, cardiovascular disease (CVD), emergency care, and pediatric cancers—for example.
- A proposed shift in the current paradigm where drugs are listed by therapeutic class/condition such as antihypertensives, sickle cell disease, ADHD, antiparasitics, influenza, pertussis, and poisonings.

Dr. Taylor-Zapata explained that the ultimate goals of the new listing process are label changes and advancement in scientific knowledge. OPPB staff have learned from the past listing process that documented experts in the fields of interest (engaged early on) are needed for input on scientific gaps and types of treatments available for conditions. Top experts in the field of pediatric hypertension can assist in the pursuit of the advancement of drugs used for pediatric care, treatment, and research. Dr. Taylor Zapata commented that the Pediatric Hypertension Treatment Working Group is the first group of experts to apply the therapeutic or condition-based approach. Pediatric hypertension experts are asked to carefully consider the following questions:

- In the area of pediatric hypertension, does off-label use of drugs in your patient population occur frequently?
- Is pediatric hypertension difficult to treat due to the lack drugs, lack of dosing information, and/or lack of safety information in your patient population?
- Is there a need for more research on specific treatments that are available or unavailable in this area of pediatrics?

Dr. Taylor-Zapata said that last year's meeting of the Pediatric Hypertension Working Group was an information gathering session. The goals of the 2005 meeting were to:

- Discuss where we are
 - In the process of defining pediatric hypertension and its associated risks
 - What is the natural history of hypertension in pediatrics?
- Discuss what we need
 - Risk factors—what to do with at-risk populations
 - Treatment strategies
- Discuss how to get what we need
 - The role and design of clinical trials
 - Outcome measures
- Discuss who do we contact/involve, who do we target
 - Disseminate the information.

The goals for the 2006 Pediatric Hypertension Working Group are to:

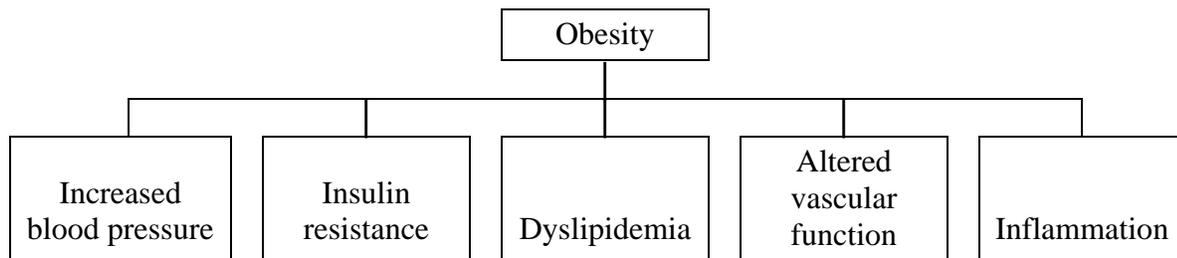
- Gather further information from a core group of experts in the diagnosis, treatment, and prevention of pediatric hypertension

- Identify gaps in knowledge in the area of pediatric hypertension and its association with obesity
- Work toward determining future directions in the areas of the diagnosis, prevalence, and treatment of pediatric hypertension.

Pediatric Obesity and Its Links to Cardiovascular Disease

Albert P. Rocchini, M.D., Director of Pediatric Cardiology, University of Michigan

Dr. Rocchini provided an overview of pediatric obesity and its links to CVD. He presented the following flow chart listing five of the major cardiovascular risk factors known to be associated with obesity:



Although cardiac hypertrophy is known to occur with obesity, it was not included in the flow chart because it is directly related to blood pressure and volume. Two questions need to be answered with regard to cardiovascular risk and obesity:

- Is there one common pathway (versus multiple related but independent pathways) leading to each of the above abnormalities?
- If so what is that pathway?

Dr. Rocchini noted that a recent confirmatory factor analysis using multiple data sets supported the hypothesis that a single factor appears—at least statistically—to be linking all of the core components of the metabolic syndrome listed above (Pladevall et al., *Diabetes Care* 2006). However, it is still not clear how obesity produces these associated conditions and whether the conditions are produced through a single common pathway or through multiple separate but independent pathways that are related in some manner. Dr. Rocchini said that multiple pathways would make treatment approaches much more complicated than a single pathway.

In his presentation, Dr. Rocchini briefly reviewed each of five cardiovascular risk factors associated with obesity and metabolic syndrome. He first explained a few relationships between hypertension and obesity:

- It has been known since the start of the 20th century that blood pressure and body weight are directly related.
- Based on Dr. Rocchini's and others' research in humans and animals, it is known that the increase in blood pressure associated with obesity is volume mediated.
- The hypertension and increase in blood volume associated with obesity are in large part mediated by the renal sympathetic nerves (Kassab et al., *Hypertension* 1995). John Hall and

colleagues at the University of Mississippi demonstrated in an obese dog model that if the kidney is denervated the dogs gain weight but no hypertension ensues.

- Although insulin resistance and the renin-angiotensin-aldosterone system play a role in the hypertension and sodium retention associated with obesity, their role is probably much less important than activation of the sympathetic nervous system (SNS).

Dr. Rocchini showed a slide of pressure natriuresis curves (urinary sodium excretion versus mean arterial pressure for nonobese, preobese, and obese human subjects). In this study, the researchers observed that the nonobese subjects were not salt sensitive. The obese subjects have an altered pressure natriuresis curve that can revert to normal with weight loss. Multiple factors are known to affect the pressure natriuresis curve, including hormones (for example, insulin and aldosterone) and the SNS.

Dr. Rocchini presented a graph showing increases in body weight and mean arterial pressure and decreases in urinary sodium excretion versus weeks (-1 to +5) on high-fat diet (2 pounds of beef fat per day) in dogs. The high-fat diet increased salt retention.

Dr. Rocchini described the results of a study on change in blood pressure and glucose uptake associated with feeding dogs a high-fat diet. He presented two graphs showing the effect of central (clonidine) versus peripheral blockade (α - + β -adrenergic) of the SNS: (1) mean arterial pressure versus weeks (-2 to +6) on high-fat diet and (2) glucose uptake versus weeks (-2 to +6) on high-fat diet. Dr. Rocchini commented that clonidine is the most actively prescribed antihypertensive medicine for children. Clonidine is, however, more frequently prescribed for ADHD and other neuropsychiatric conditions in children. In the dog model, clonidine is an effective antihypertensive and, at the same time, improves insulin resistance and blood pressure.

Dr. Rocchini characterized the relationship between insulin resistance and obesity:

- Insulin resistance occurs very rapidly in the course of weight gain.
- Insulin resistance is frequently considered in metabolic syndrome and may be the driving force that links all of the risk factors in metabolic syndrome.
- Insulin resistance is selective; for example, despite being resistant to glucose uptake obese adolescents still have sensitivity to the renal sodium retaining effects of insulin.
- Insulin resistance correlates with the lipid abnormalities in patients with the metabolic syndrome (Steinberger et al., *Am J Cardiol* 2002).

Dr. Rocchini depicted the time course of insulin resistance in the dog model. The graph showed a dose-response curve (glucose levels versus insulin levels at 0, 1, 3, and 6 weeks on a high-fat diet. In this study, insulin resistance increased after 1 week and peaked at 3 weeks. Dr. Rocchini described the insulin resistance response to fat intake as a very rapid phenomenon in this animal model, and it may be similar in humans.

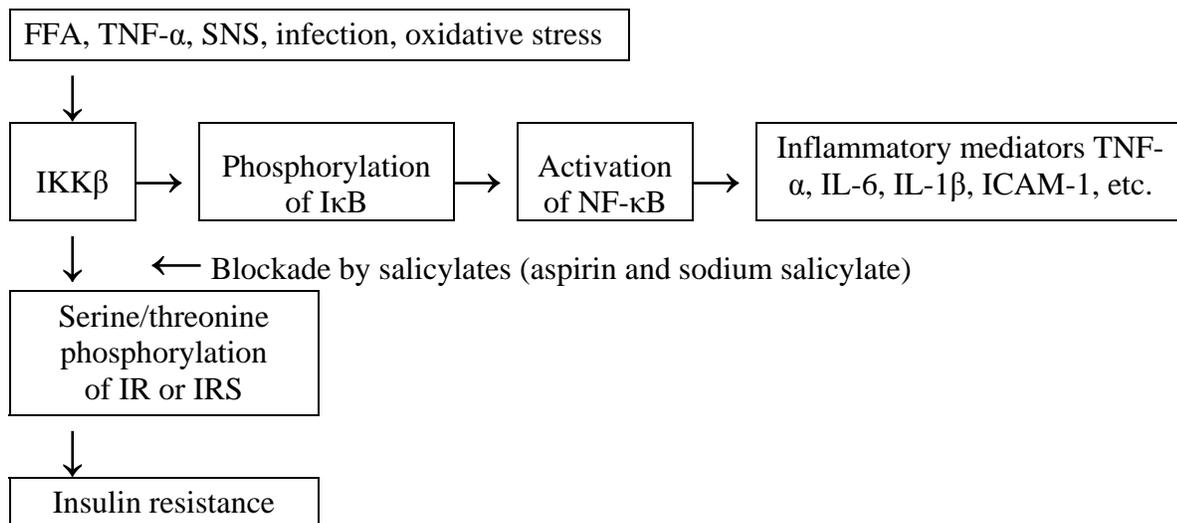
Next, Dr. Rocchini showed two bar graphs demonstrating selective insulin resistance in obese and nonobese adolescent subjects: (1) percentage change of urinary sodium excretion as an index of insulin's ability to cause the kidney to retain salt and (2) glucose uptake as an index of insulin

sensitivity. In this study, the obese subjects were shown to be very insulin resistant compared with nonobese subjects, yet the urinary-retaining effects of insulin in both groups were the same.

Dr. Rocchini described what is currently known about insulin resistance as the cause of the metabolic syndrome: Insulin resistance does not cause hypertension, and hypertension does not cause insulin resistance. The results of several classic studies showed that:

- Gastric bypass surgery acutely decreases both blood pressure and insulin resistance; but over 5–10 years of follow-up—despite maintenance of weight loss—blood pressure gradually increases to the pre-gastric bypass levels, yet insulin resistance does not return. These results bring into question the effect of insulin resistance as the mediator of hypertension.
- In dogs and humans, aspirin blocks insulin resistance but does not prevent hypertension.
- Diuretics and sodium restriction prevent hypertension but do not improve insulin resistance.

Based on data from a variety of studies, Shoelson et al. (*Int J Obesity* 2003) developed a hypothesis of insulin resistance involving the IKK β /I κ B/NF- κ B, as follows:



Dr. Rocchini and colleagues tested Shoelson's hypothesis in the dog model. The effects on blood pressure, in 8 dogs fed a high-fat diet, by preventing insulin resistance with aspirin were depicted in two graphs: (1) mean arterial pressure versus weeks (–2 to +6) on a high-fat diet and (2) glucose levels versus weeks (–2 to +6) on a high-fat diet. The results showed that aspirin has no effect on blood pressure but almost completely blocks insulin resistance. This study suggests dissociation between insulin resistance and hypertension.

Dr. Rocchini described the lipid abnormalities associated with metabolic syndrome:

- The characteristic lipid abnormality associated with the metabolic syndrome is increased in triglycerides, decreased in high-density lipoprotein (HDL)-cholesterol, and an increase in the number of atherogenic-dense low-density lipoprotein (LDL) particles.

- Two of causes of elevated triglycerides are through enhanced hepatic very-low-density-lipoprotein synthesis and through a defect in very-low-density-lipoprotein removal (through reduced LPL activity).
- An increased rate of degradation of the apoprotein AI (the major lipoprotein in HDL-cholesterol) is believed to be a major cause for the reduced level of HDL-cholesterol observed in many insulin resistant subjects.
- There are many genetic factors that modulate the lipid profile. For example, the Apo E polymorphisms E₂ and E₃ have dyslipidemia, yet the E₄ polymorphism does not have the hypertriglyceridemia associated with abdominal adiposity and insulin resistance. Similarly, Apo B-100 gene Eco RI (+/-) men are more prone to hyperapoprotein B in the presence of visceral adiposity, whereas (+/+) men are not.

Dr. Rocchini explained that obesity is associated with impaired endothelial function. In humans and animals, impaired flow-mediated vasodilation in peripheral and coronary vascular beds has been documented by numerous investigators. Endothelial dysfunction can be prevented or treated by improving insulin resistance, blocking the SNS with centrally acting drugs such as moxonidine or clonidine, and using antioxidant therapy with oxygen free-radical scavengers.

In two graphs, Dr. Rocchini depicted the endothelium-dependent dilation of coronary artery before and after high-fat diet ($n = 5$ animals): (1) absolute coronary blood flow (CBF) versus acetylcholine and (2) percentage change CBF (mL/min) versus acetylcholine. In these animals, nitroprusside infusions increased CBF to the same degree before and after starting the high-fat diet. In three of these animals, after 6 weeks of the high-fat diet, the cell-permeable oxygen free-radical scavenger trion (sodium dihydroxybenzene disulfonate) was administered into the coronary artery. Ten minutes after starting trion, the response to grade infusions of acetylcholine was evaluated. Trion normalized the CBF response to acetylcholine. This result is very similar to what has been reported in animal models of flow-mediated vasodilation associated with congestive heart failure.

Another study examined the effect of 20 seconds of coronary occlusion on reactive hyperemia in dogs ($n = 6$) fed a high-fat diet with and without clonidine. Within 1 week of starting the high-fat diet, there is a 50-percent reduction in coronary flow-mediated vasodilation. This reduction is prevented with clonidine.

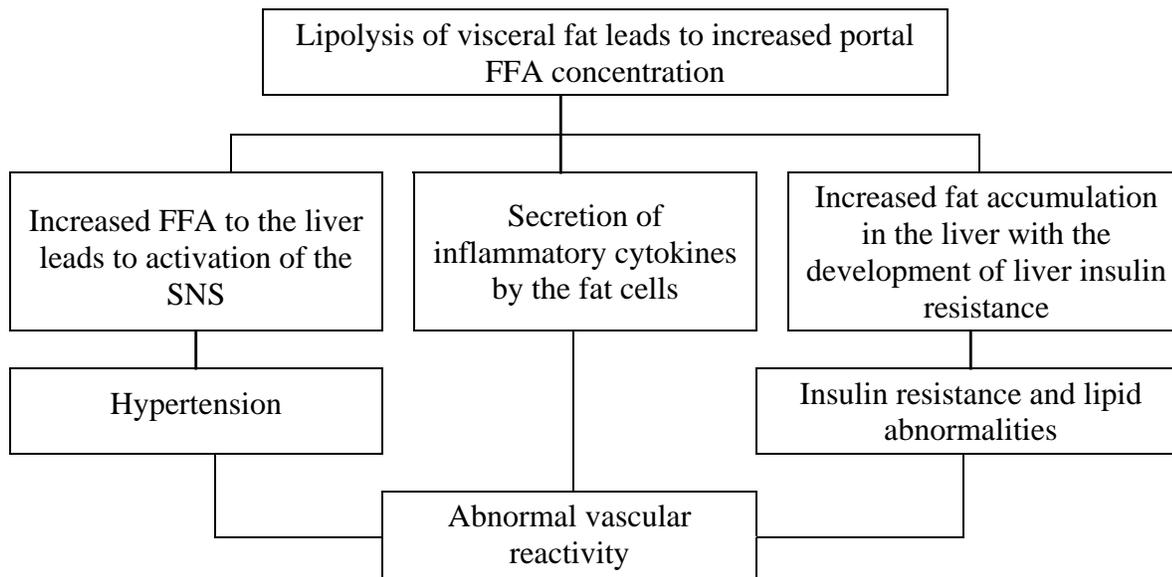
Dr. Rocchini characterized the association of inflammation and the metabolic syndrome:

- Pediatric and adult patients with the metabolic syndrome have evidence of chronic inflammation. Chronic inflammation is a known pathogenic feature of atherosclerosis. The known markers of inflammation in obesity include increase in:
 - C-reactive protein
 - Serum cell adhesion molecules
 - ICAM-1 and VCAM-1 metalloproteinases
 - Monocyte chemoattractant proteins
 - Proinflammatory cytokines such as IL-6, TNF- α .
- The question that needs to be answered is whether inflammation is cause or effect.

There are three potential mechanisms of the metabolic syndrome:

- Portal hypothesis—A high rate of lipolysis of visceral adipose tissue leads to increased delivery of free fatty acids (FFAs) to the liver via the portal vein, thus contributing to increased fat accumulation and hepatic and then whole body insulin resistance (Bergman, *Am J Physiol* 2005). Blood pressure is increased by activation of the SNS (Grekin et al., *Am J Physiol* 1997).
- Inflammatory hypothesis—Visceral fat secretes several substances including TNF- α and resistin. There is a decrease in adiponectin and an increased oxidative stress. Alternatively, FFAs activate the IKK β /I κ B/NF- κ B axis leading to the development of insulin resistance and hypertension (Shoelson et al., *Int J Obesity* 2003).
- The SNS hypothesis—There is increased central SNS activity either through activation of α 2-adrenergic receptors or through inducing oxidative stress that leads to the development of insulin resistance (Rocchini et al., *Hypertension* 2005).

Dr. Rocchini presented the following diagram to explain the portal hypothesis:



Bergman et al.'s data suggest that this hypothesis is possible by demonstrating increased gene expression of lipid accumulation and lipolysis in visceral fat and elevated rate-limiting gluconeogenic enzyme expressions in the liver. However, there are no data to document an increase in portal FFA.

Inflammatory hypothesis involves the relationships among the following conditions:

- Adipose tissue
 - TNF α
 - Adiponectin

- NF- κ B activation
- Glucose and FFA
- Oxidative stress
- Adhesion molecules and inflammatory cytokines
- Hypertension
- Dyslipidemia
- Insulin resistance
- Endothelial dysfunction.

Shoelson's data suggest that this pathway is active in the production of insulin resistance. However, there are no data demonstrating that increased TNF α or decreased adiponectin precede the development of insulin resistance or any of the other parts of the metabolic syndrome.

The SNS hypothesis involves the relationships among the following:

- High-fat diet–induced obesity hypertension
- Increased central nervous system activation
- Hypertension and activation of renin-angiotensin-aldosterone system
- Activation of NF- κ B
- Increased production of oxygen free radicals
- Insulin resistance
- Dyslipidemia
- Altered endothelial function.

Rocchini et al.'s data demonstrated that central sympathetic agents can prevent both insulin resistance and hypertension in an obese dog model and that aspirin can block the insulin resistance and not affect the hypertension. However, the research has not shown how a high-fat diet activates the SNS. Rocchini et al.'s data could also be explained by central sympathetic agents—especially clonidine—that decrease FFA concentrations. In some ways, activation of the SNS could be step 2 in the pathway from obesity to cardiovascular risk. Step 1—the trigger to step 2—is not known. One clue may be found in dietary-induced thermogenesis; that is, thermogenesis begins within minutes of food consumption.

Questions that need to be answered include:

- What pharmacologic agents are best suited to prevent and reduce cardiovascular risk in obese adolescents with the metabolic syndrome?
- What antihypertensive agents are best for treating the obese individual? Diuretics, ACE inhibitors, calcium channel blockers, or central sympathetic agonists?
- What is the role of PPAR γ in treating hypertension in the metabolic syndrome?
- What is the role of statins in the treatment of hypertension in the metabolic syndrome?
- What is the role of NF- κ B antagonists in the treatment of hypertension in the metabolic syndrome?

Dr. Rocchini concluded his presentation by stating that treatment providers currently do not know which drug is best to treat obesity-mediated hypertension in children.

In a subsequent question-and-answer session, Dr. Rocchini explained that simple reduction in body weight is a great approach to reduce blood pressure, but it has not proven to be a realistic or successful approach. Children across America continue to become more obese despite all efforts. In response to a question from Abraham Karkowsky, M.D., Ph.D., Dr. Rocchini replied that puberty and especially the associated androgens are known to affect insulin resistance and lipids. In addition, blood pressure increases during puberty and levels off with adulthood. In response to another question, Dr. Rocchini said there are no data on the cascade of acute changes after a fatty meal in dogs with gastrectomies. Jonathan Sorof, M.D., noted that an observational study of school children showed that hypertensive children had higher heart rates than normotensive children, and that obese children had higher heart rates than nonobese children. Children who were obese and hypertensive had the highest heart rates. The elevated heart rates were considered rough markers of increased SNS activity. Dr. Rocchini suggested a possible mechanism for obesity-related hypertension: elevated FFAs trigger inflammation, SNS activation, or leptin production.

Obesity-Associated Hypertension in the Young

Bonita Falkner, M.D., Professor of Medicine and Pediatrics, Thomas Jefferson University

Dr. Falkner provided an overview of studies of overweight and high blood pressure in the young. The purpose of her presentation was to explore whether obesity-associated hypertension is a unique condition in the young.

A recent study by Thomas et al. (*Hypertension* 2005) determined the hazard ratio for CVD mortality with respect to body mass index (BMI) and other factors. The results from about 200,000 subjects from France showed that hypertension with a high BMI increases mortality. Compared with a reference group (BMI of 18.5–24.9 kg/m²), the hazard ratio increased for subjects with BMI greater than 25 kg/m² and increased in an ascending order with the following factors:

- Without acute renal failure (ARF)
- With diabetes mellitus (DM)
- With hypercholesterolemia (Hch)
- With hypertension (Htn)
- With Htn and Hch
- With Htn and DM
- With three ARF.

Dr. Falkner next presented data from the 1988–1994 National Health and Nutrition Examination Survey (NHANES) and the 1999–2000 NHANES. An analysis of overweight prevalence by race/ethnicity (non-Hispanic White, non-Hispanic Black, and Mexican-American) for adolescent boys and girls (ages 12–19 years) showed trends of increasing obesity for all groups from the 1988–1994 NHANES to the 1999–2000 NHANES. An analysis of mean systolic blood pressure

among children by race/ethnicity (non-Hispanic White, non-Hispanic Black, and Mexican-American) showed trends of increasing blood pressure for all groups from the 1988–1994 NHANES to the 1999–2000 NHANES. The increases in blood pressure are associated with increases in BMI. Current data suggest that about 17 percent of American children are overweight. In addition, overweight disproportionately affects minority children.

A study by Sorof and Daniels (*Hypertension* 2004) using high school screening data demonstrated increasing rates of children with hypertension with increasing BMI percentile. The results showed that about 34 percent of children with a BMI in the ≥ 95 percentile are hypertensive. Dr. Falkner commented that high BMI and high blood pressure are two components of metabolic syndrome.

Dr. Falkner presented data from 18,000 children who were examined in pediatric primary care practices in Pennsylvania. Data were gathered from both boys and girls. Mean systolic blood pressure was determined by age and BMI in males in four age groups (2–5 years, 6–10 years, 11–15 years, and 16–19 years). All BMI groups (<85th percentile, 85th–95th percentile, and ≥ 95 th percentile) showed increased blood pressure with age. For each group, higher BMI was associated with higher blood pressure; blood pressure increases were greatest in the ≥ 95 th percentile group. Mean systolic blood pressure by age and BMI was determined for the same groups in females. All BMI groups (<85th percentile, 85th–95th percentile, and ≥ 95 th percentile) showed increases with age. Blood pressure increases for the 95th percentile group were greater than for the other two groups. The increases for females were not as great as those for males.

The Pennsylvania data were further analyzed to determine the prevalence of systolic hypertension in boys in the four age groups. All BMI groups (<85th percentile, 85th–95th percentile, and 95th percentile) showed increases with age. However, systolic hypertension increases for the 95th percentile group were greater than for the other two groups. Prevalence of systolic hypertension for the 95th percentile group was greatest in the 11–15 year age group (about 20 percent). The prevalence of systolic hypertension was also determined in the girls. All BMI groups (<85th percentile, 85th–95th percentile, and 95th percentile) showed increases with age. However, systolic hypertension increases for the 95th percentile group were greater than for the other two groups. Prevalence of systolic hypertension for the 95th percentile group was greatest in the 16–19 year age group (about 20 percent).

Boyd et al. (*Pediatrics* 2005) examined the prevalence of high blood pressure by obesity severity. Moderately obese males—both prehypertensive and hypertensive—had a greater prevalence of high blood pressure than did moderately obese females. The prevalence of high blood pressure was greatest in severely obese males—both prehypertensive and hypertensive.

Daniels et al. (*Circulation* 1998) studied left ventricular hypertrophy (LVH) in children with primary hypertension. In 130 children with blood pressure greater than the 90th percentile, about 6 percent had LVH (LVH = left ventricular mass index $> 51 \text{ gm/m}^{2.7}$). About 6 percent of the children in the 90th–95th percentile group had LVH, whereas about 30 percent of children in the 95th–99th percentile group had LVH. Most of the children in this study were also overweight.

Mulè and Cerasola (*J Clin Hypertens* 2006) assessed adult nondiabetic hypertensives with and without metabolic syndrome. The study looked at four groups: (1) left ventricular (LV) mass indexed for body surface area, (2) LV mass indexed for height, (3) relative wall thickness, and (4) left atrial dimension. In all four groups, the rate of LVH was greater for hypertensive subjects with metabolic syndrome than for hypertensive subjects without metabolic syndrome.

With regard to the outcomes of obesity-related hypertension, Dr. Falkner presented autopsy data from the Bogalusa Heart Study (Berenson et al., *N Engl J Med* 1998) showing the association of risk factors with vessel pathology (aortic lesions). The results revealed that the percentage of aortic lesions (fatty streaks) increased with the number of standard risk factors such as hypertension, lipid abnormalities, and adiposity. Each of the risk factors are a component of metabolic syndrome. The subjects were young persons who had suffered accidental deaths.

Dr. Falkner presented data on the progression of prehypertension to hypertension over a 2-year period in children ages 13–15 years.

- Girls
 - At 13, about 6 percent became hypertensive
 - At 14, about 12 percent became hypertensive
 - At 15, about 17 percent became hypertensive
- Boys
 - At 13, about 14 percent became hypertensive
 - At 14, about 16 percent became hypertensive
 - At 15, about 12 percent became hypertensive.

A further analysis of the data in this study revealed that increases in BMI were driving the progression from prehypertension to hypertension.

Dr. Falkner said that recent study results suggest that obesity-related hypertension is a significant and potentially lethal problem in adults and that it is present and identifiable in the young. Obesity-related hypertension may be causing target organ damage in the young. Dr. Falkner concluded her presentation by depicting a vascular injury timeline. As inflammation, hypertrophy, and fibrosis increase, the following conditions manifest:

- From first decade
 - Foam cells
 - Fatty streaks
- From third decade
 - Intermediate lesion
 - Atheroma
- From fourth decade
 - Fibrous plaque
 - Complicated lesion/rupture.

In a question-and-answer session, Dr. Falkner said that, in the studies presented, almost all blood pressures in children were measured with auscultation. Dr. Sorof commented that, based on his

research, it is his belief that hypertension is the number one health problem in America's children. In response to a question about normal blood pressure for age and body size/stature, Dr. Falkner replied that there is a normal versus ideal distribution. The values that are considered normal have been increasing from generation to generation as average body weights have increased. There are new/changed growth curves for children's height and weight, and there are differences for men and women (for example, women generally have lower blood pressure than men). Dr. Rocchini reiterated that weight loss leads to decreases in blood pressure, even if the blood pressure is in the normal range. In a final comment, Dr. Falkner noted that some obese people are normal with regard to other risk factors. Obese people without higher blood pressure do not have higher rates of morbidity and mortality.

Pediatric Hypertension Trials Network (PHYTN)

Ronald J. Portman, M.D., Professor and Director, Division of Pediatric Nephrology and Hypertension, University of Texas-Houston, Medical School

Dr. Portman acknowledged his Pediatric Hypertension Trials Network (PHYTN) colleagues: John S. March, M.D., M.P.H., and Barry Magnum, both of the Duke University Medical Center, Durham, NC. The purpose of Dr. Portman's presentation was to provide an overview of the proposed PHYTN. The first part of his presentation provided background information on pediatric clinical research; the second part described the details of PHYTN. Dr. Portman began by characterizing pediatric hypertension research to date:

- Relatively small clinical trials from academia
- Four task force reports on blood pressure diagnosis, evaluation, and management
- European studies in ambulatory blood pressure monitoring
- Several large single-center experiences such as the Bogalusa Heart Study (also known as the Muscatine Heart Study)
- Most studies performed from referral populations in university settings
- Prevalence of hypertension suggests that there are many more patients than are identified and referred
- FDAMA
- Pediatric Research Equity Act (PREA)
- BPCA.

Dr. Portman posed several questions concerning pediatric hypertension:

- How do treatment providers prevent hypertension from occurring?
- What are the long-term consequences of hypertension?
- How do treatment providers best diagnose those at risk?
- What is the best method of treatment?
- How long do treatment providers need to treat hypertension?
- Is hypertension curable?

Dr. Portman characterized the conflicting values and common interests of university and industry with regard to disease treatment:

- University

- Knowledge for knowledge's sake
 - Teaching
 - Research
 - Service
 - Economic development
- Academic Freedom
- Open discourse
- Industry
 - Management of knowledge for profit
 - Profits
 - Product research and development
 - Confidentiality
 - Limited public disclosure.

The overlap between university and industry efforts allows commercialization of new and useful technologies.

According to David Sackett, M.D., "Evidence-based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients." Evidenced-based medicine requires best evidence that is:

- Clinically meaningful
- Generalizable (few filters)
 - Real world patients
 - Real world doctors
 - Real world treatment(s)
 - Real world outcomes
- Replicable.

Dr. Portman noted the failure of relatively small, short-term clinical trials for drug safety and efficacy:

- COX-2 inhibitors and cardiovascular risk
- Cardiac arrhythmia suppression trial shows short-term benefit; long-term increase in mortality
- Acetylsalicylic acid (also known as aspirin) and primary prevention of cardiovascular risk; increased stroke risk
- ADHD and cardiovascular risk
- Phenylpropanolamine and ephedra and cardiovascular risk
- Selective serotonin reuptake inhibitors (SSRIs) and adolescent suicide.

Dr. Portman asked the meeting participants to imagine the possibilities of the following:

- A large network of community physicians seeing patients in general practice settings able to participate in practical clinical trials (PCTs)
 - Remember—a small fraction of hypertension patients are identified or referred
 - Need to do the research where the patients are located

- NIH can facilitate dialogue with all stakeholders to frame questions and run PCTs
- FDA permits using PCTs to change labeling language
- Industry provides stable funding for the network
- The proposal is that industry, NIH, and the Foundation for NIH would all together provide funding for PCTs on the network
 - Use of BPCA funding.

According to Richard Peto, PCTs, which are almost always larger and always simpler than typical randomized clinical trials (RCTs), “provide reliable estimates of health outcomes applicable to a broad patient base treated under usual clinical conditions without bias.”

The characteristics of PCTs (March et al., *Am J Psychiatry* 2005) include:

- A straightforward clinically relevant question
- Representative sample of patients and practice settings
- Sufficient power to identify modest clinically relevant effects
- Randomization to protect against bias
- Clinical uncertainty regarding the outcome of treatment at the patient level
- Best clinical practice diagnostic assessment
- Best clinical practice treatments
- Simple and clinically relevant outcomes
- Limited subject and investigator burden
- High value per dollar spent.

The types of PCTs include:

- Comparison between an active treatment and a control or a comparison treatment
- Comparisons between proven treatments
- Comparisons between a proven treatment and a widely used but understudied alternative treatment
- Treatment addition studies involving either augmenting or adjunctive treatments
- Long-term follow-up for effectiveness outcomes
- Long-term follow-up for safety outcomes
- Comparison of treatment algorithms
- Treatment to response using tailored modules
- Randomization to different length maintenance baselines
- Equipose model for multiple drug trials (modified Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial [ALLHAT]).

Dr. Portman characterized a large, simple trial:

- Large in this case means:
 - The random allocation of hundreds or even thousands of patients
 - In hundreds of clinical centers
 - To different treatments
 - As they are delivered in community settings

- Simple means that the number of data elements (and, hence, subject and investigator burden) is sufficiently small so as to
 - Not discourage provider or patient participation
 - Maximize the number of subjects per dollar spent.

Dr. Portman presented a table that compared study characteristics such as research questions, setting, sample size, power for difference, other interventions, control, assessments, and data collection and monitoring with PCTs and studies of efficacy, efficacy/effectiveness, and practice research.

Dr. Portman described the model and goals of the Child and Adolescent Psychiatry Trials Network (CAPTN; www.captm.org):

- Model—Children’s Oncology Group (COG)
 - 95 percent of children with cancer in 500 centers are involved with COG and funded by the National Cancer Institute
- RCTs of widely used treatments for which empirical evidence is lacking.
- Long-term safety of commonly used drug treatments
- 200 independent child psychiatrists currently in the network; 70 percent in private practice; 17 training centers; 30 academic centers
- Web-based learning and data entry
- Investigator-initiated research ideas encouraged
- First study is a safety and adverse events monitoring of SSRIs
- About \$1,500 per patient compensation over length of study.

Dr. Portman listed the organizational elements of PHYTN:

- Executive committee
 - Steering committee
 - Internal scientific advisory committee
 - Data safety and monitoring board
 - International Pediatric Hypertension Association (IPHA)
- Operational cores
 - Operations core (Duke Clinical Research Institute)
 - Research methods core (University of Texas-Houston)
 - Principal research core (University of Texas-Houston)
 - Network development core (Duke Clinical Research Institute)
- Administration
- Project management
- Site management
- Data management
- Statistical services
- Web-based services
- Randomization/pharmacy
- Budgets and contracts

- Quality assurance
- Regulatory affairs
- Communications.

The benefits of PHYTN to pediatricians include:

- Opportunity to perform research—be involved in “making a difference”
- Continuing medical education credits
- Personal and staff education
- Cutting edge of technology and management
- Reasonable source of income.

Dr. Portman provided an overview of PHYTN; its development included:

- Recruit academic and private practice groups into the network
 - IPHA (academic participants)
 - Identify primary care pediatricians
 - Wide geographic distribution
 - Urban and rural settings
 - Solo, multipediatrician practices, multispecialty practices, network of physicians
 - Computer literate
 - Interested in learning about research.

Practices were identified as follows:

- Blast email sent from IPHA to all pediatricians with known email addresses—about 11,000 from the American Academy of Pediatrics
- Received responses from 217 practices representing a minimum estimate of more than 500 pediatricians who would represent more than 1,000,000 children
- Biases selection process to provide “best case scenario”—pediatricians, internet access, interested.

Dr. Portman described the PHYTN practices as follows:

- 217 practices
- 37 states with respondents; 14 none
- 108 urban areas (with a population of more than 200,000)
- 76 rural areas; 33 not stated
- At least 72 in private practice
- At least 29 multiple pediatricians
- At least 488 pediatricians in the network.

Dr. Portman characterized the PHYTN practices as follows:

- Dual purpose
 - Characterize practices for later selection
 - Diverse practice type, geographic distribution, setting
 - Collect data on current practices of blood pressure measurement and management and determine knowledge of and compliance with 4th Working Group report.

Dr. Portman listed some of the questions about (1) diagnosis of hypertension in children and adolescents, (2) practice demographics, and (3) compliance with 4th Working Group that were included in the survey:

- Information about blood pressure measurement
 - In general, at what age do your patients start having the blood pressure measured as part of their vital signs?
- Measurement questions
 - Do you use the bell or diaphragm of the stethoscope when checking blood pressure to listen for Korotkoff sounds?
 - What Korotkoff sound do you consider systolic blood pressure?
 - What Korotkoff sound do you consider diastolic blood pressure?
 - Can the Korotkoff sound for diastolic blood pressure be variable in children?
- Practice demographics
 - What type of physician are you?
 - What type of practice do you work in?
 - Is your practice solo? Partnership? Group practice? Other?
 - If you practice in a group practice, how many pediatricians are your practice?
- Compliance with 4th Working Group
 - How familiar are you with the *Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents*?
 - Approximately how many patients did you diagnose with hypertension in the last year?
 - Please estimate the percentage of patients in your practice with hypertension.

Additional information on the survey and a listing of the questions can be found at:
<http://www.surveymonkey.com/s.asp?u=998941581685>.

Dr. Portman summarized the state of pediatric hypertension research as follows:

- Truly clinically relevant evidence is mostly lacking.
- Current trial designs do not generalize and fail to give researchers the clinical information that would truly help with patient care.
- Current trials are expensive and slow to complete.
- Large, simple trials address these deficits and, in doing so, promote dissemination of evidence-based practice.

Dr. Portman summarized the advantages of PHYTN:

- Patients cared for by their primary care physicians
- Focus on identification of hypertension and other cardiovascular risks (obesity, lipids, metabolic syndrome)
- Focus on detection of hypertension, evaluation, and management including therapeutic lifestyle change (TLC)
- Education for primary care that can lead to a “snow-ball” effect for the practice community
- Better detection and early identification in a group of patients who may benefit from early intervention

- CVD prevention is to the 21st century what immunizations were to the 20th century (CVD is a national epidemic, with many unanswered questions.)
- Large numbers of patients in simple, practical clinical trials
- Cost-effective, well-trained, organized network of enthusiastic investigators for use by NIH, academia, industry and FDA
- Answers provided for clinically relevant questions.

In a subsequent question-and-answer session, Julie R. Ingelfinger, M.D., stated that optimized interventions and medication doses are important for pediatric clinical trials, but they are often not known. Because of this circumstance, Dr. Ingelfinger asked whether pediatric researchers are ready for PHYTN. Dr. Portman emphasized the need to adequately define a pediatric network, to collect valid data, and to characterize network practices as an educational process. Dr. Ingelfinger described the network practices of Australian practitioners, who learn in medical school the value of research participation. Practitioners' participation in research is engrained in Australian medical culture. In response to a question about the survey's time frame, Dr. Portman replied that practitioners' information will be collected for about 12 months, depending on funding. Dr. Sorof—who was a cofounder of IPHA with Dr. Portman—explained that the fundamental defining feature of successful research networks such as COG, CAPTN, and the ESCAPE group (a European-based collaborative pediatric nephrology research network) is the involvement of medical specialists, not regular practicing pediatricians outside of academia. Dr. Sorof noted that treatment providers who successfully enroll patients in clinical trials are generally not providing “well care.” Successful providers are often treatment providers that operate obesity or hypertension clinics. Dr. Rocchini suggested that a regional network system (that is, a “hub and spoke concept”) might provide an effective structure with a designated research advocate—a specialist who is passionate about the cause and who will serve as a regional “captain.” Mark S. Schreiner, M.D., commented PCTs involve questions of effectiveness as opposed to efficacy. First there must be evidence of efficacy and the right dose; then a study can determine the effectiveness of the dosing regimen. Dr. Portman noted that a pediatric version of ALLHAT, with thousands of subjects, may not be necessary to determine which drugs are most effective in treating pediatric hypertension.

Part 1: Discussion of Topics

Given the meeting's emphasis so far on pediatric obesity, Dr. Taylor-Zapata posed the following questions to begin this discussion session:

With the increasing role of obesity in children and its secondary effects such as hypertension, what role should nonpharmacological interventions such as weight loss and exercise play (that is, TLC) in antihypertensive trials? Are there statistically meaningful covariates (for example, changes in BMI) that should be monitored in an antihypertensive drug trial? If so:

- How would these nonpharmacological interventions affect enrollment criteria?
- How do you take these interventions into account in trial design?
- How would these interventions affect the conduct of short- and long-term studies?

Dr. Falkner described obesity as a childhood problem, it is a public health problem, and it is a medical problem because of obesity-associated comorbidities. Therefore, TLC is an appropriate nonpharmacological intervention and should be provided to the extent possible. Dr. Falkner said that nonpharmacological interventions can be managed as covariates in pediatric trials. Dr. Rocchini concurred and added that nonpharmacological interventions can provide the baseline for subsequent drug therapies. He noted that body weight and BMI changes are easy surrogates to measure, and pedometers are easy tools to provide some indication of activity. Body weight, BMI, and activity can be used to measure compliance with TLC. Once this base is established, a clinical trial can be planned. Dr. Ingelfinger agreed that establishing a baseline is important, but she asked how long such a baseline would need to be maintained. Entry measures would be important for any clinical trials.

Because the population that is being studied is predominantly obese (about 75 percent), Dr. Sorof commented that it does not make sense to combine in a trial children with documented secondary hypertension with children with obesity-related hypertension. He said that because these disease conditions are so different, their responses to drug therapies will be much different. Therefore, any study should include only children with obesity-related hypertension, not all children with hypertension.

Dr. Portman remarked that TLC for a child has been a uniform failure when obesity is a family lifestyle. He emphasized that there may be little change in obesity and hypertension with just nonpharmacological interventions and TLC. The changes in obesity and hypertension in children are often center-specific. TLC is currently not defined or standardized. There is little agreement on the specific changes that need to be implemented.

Dr. Schreiner said that efficacy trials could be short-term. These trials would establish dose-response curves to determine appropriate medication doses. Once the doses are established, longer term head-to-head comparative studies (that is, effectiveness studies) could be conducted.

Dr. Karkowsky explained that data from adults studies have shown that confounding treatments will alter the affect of a single other treatment. Investigators must therefore ensure that the confounding treatments are at steady state before altering the next intervention. Another approach in adult studies is the factorial design, in which two modalities are tested concurrently. Factorial design studies require larger sample sizes and can include multiple factors (such as moderate TLC versus intense TLC with drug versus no drug or even different drug doses), but investigators need to know the question they are trying to answer. The study design will depend on the question that investigators want to answer. Dr. Schreiner said the factorial design would be appropriate for studying the efficacy of diuretics. He noted that all of the written requests that FDA issued through FDAMA suggested a factorial design for diuretics.

The meeting participants then moved on to the next set of questions:

What are the roles of the currently listed BPCA drugs for the indication of hypertension?
What would be your priorities for studying these drugs? If not these drugs, what would

be your priority drugs for this indication? In your responses, please indicate the potential population of patients for study and feasibility of study designs. BPCA diuretics indicated for hypertension include:

- Labetol
- Bemetanide
- Spironolactone
- Furosemide
- Hydrochlorothiazide.

Dr. Sorof mentioned his experience with the ZIAC study (a combination of bisoprolol fumarate and hydrochlorothiazide, which was submitted to FDA for labeling but was rejected because it is a combination drug). FDA explained that each component needs to be studied separately. Dr. Sorof said that this drug and other combination diuretics should be studied using factorial designs. With this approach, multiple questions can be answered at one time.

Dr. Taylor-Zapata asked the attendees representing FDA if there are barriers to labeling the pediatric combination drugs. Dr. Karkowsky explained the FDA's algorithm for labeling single drugs. Normally, two clinical trials are required for an adult antihypertensive drug that requires labeling. For children, if the drug's indication is already incorporated in the labeling, then a single clinical trial is sufficient. Problems arise when deviations from the adult labeling occur. For a combination drug, the clinical trials must demonstrate that each component contributes to the overall effect of the drugs; each component must improve outcomes. Dr. Karkowsky said that the safety and efficacy of each monotherapy must be demonstrated before FDA will consider the combination of drugs. Alan M. Shapiro, M.D., Ph.D., noted that one of the problems with fixed-dose combination drugs is that the dosages cannot be appropriately reduced for children.

Rae-Ellen W. Kavey, M.D., M.P.H., agreed with the suggestion that obesity-related hypertension be studied by itself, not combined with secondary hypertension. She observed that, to her knowledge, diuretics have not been studied alone in pediatric hypertension. She said that beta blockers should be effective in this patient population. Dr. Kavey suggested designing trials to determine the efficacy of diuretics and beta blockers—drugs that are already being prescribed for pediatric patients. Dr. Rocchini commented that simply treating hypertension may not be the best approach for obese patients. Treating one risk factor may change other risk factors, which may then require treating. The best drug or drug combination for treating obesity-related hypertension is not known. Dr. Ingelfinger noted that there have been no studies of adverse metabolic events with diuretics, and Dr. Falkner noted that there is no information on diuretic dosing in children. Donald L. Batisky, M.D., said that finding adequate numbers of pediatric patients has been an obstacle to such studies. Dr. Portman said that a national network would be able to overcome enrollment obstacles, but resources are needed for a pediatric network.

Dr. Taylor-Zapata asked:

What are the important outcomes measures in clinical trials of pediatric hypertension?

The meeting participants agreed that the initial, short-term outcome measure would be reduction in blood pressure. Dr. Schreiner explained that blood pressure is, however, a surrogate measure, as are adverse events. More important measures are long-term, end-stage outcomes such as reduced risk factors, morbidity, and mortality 20 or 30 years after pediatric interventions. The meeting participants discussed the fact that there are few data to demonstrate either disease regression or progression versus treatment or nontreatment. Dr. Sorof commented that BMI may better serve as a surrogate outcome measure in treating obesity-related hypertension.

In response to a discussion of the relative importance of determining the right drug to treat certain pediatric conditions such as obesity-related hypertension or to get drugs properly labeled for pediatric indications, Dr. Mattison said that it is more important to publish the results of pediatric clinical trials so that drug information is in the literature. Practitioners need to know which drugs are the right drug for particular patients with particular conditions. Proper labeling is important, but the issue of developing best clinical practices and having them implemented in regular pediatric practices is very important as well.

Several meeting participants countered that it is more important to move the scientific field forward before practice can be changed. The first step is to gather pharmacokinetic data to support the need for clinical trials. Fundamental data from clinical trials can then be submitted to FDA to change labeling. The data need to be interpretable so that evidence-based decisions can be made. Sufficient numbers of patients, appropriate endpoints, and good safety data all contribute to the written-request process. Dr. Karkowsky emphasized the need for adequate data to initial pediatric clinical trials. He noted that only 3 of 10 drugs used to treat children have dosing information.

The meeting participants briefly discussed the value and issues of placebo-controlled trials to close the knowledge gap of pediatric drugs. Dr. Karkowsky explained that the FDA will consider information gathered in placebo-controlled trial. These trials are acceptable for several reasons, but placebo can be considered minimal risk. Dr. Karkowsky clarified the details on what constitutes a successful clinical trial. Essentially, the trial needs to clearly demonstrate that a drug either works or does not work.

Dr. Rocchini reiterated that there is little information on the efficacy of many monotherapies. The efficacy of diuretics alone, ACE inhibitors alone, and calcium channel blockers alone for the treatment of hypertension and metabolic syndrome is not known. ShaAvhrée Y. Buckman, M.D., Ph.D., asked how much reduction in blood pressure would be required in children to indicate “successful” treatment. A 3-mL diastolic reduction is not considered a relevant change, whereas a 5-mL systolic reduction would be relevant. The meeting participants agreed with this value, and they agreed that, because of the greater variability and spurious information, excluding younger children (1–5 years old) would be appropriate. Dr. Karkowsky agreed that a primary endpoint of systolic blood pressure is acceptable.

Part 2: Open Discussion

Dr. Taylor-Zapata said that there are well-defined strategies for treating hypertension in adults. She asked the meeting participants if there should be similar strategies for treating pediatric hypertension. Dr. Batsky commented that labeling of pediatric drugs should precede the development of treatment strategies. Dr. Portman noted that not all pediatric hypertension is the same; treatment strategies depend on causes and disease conditions. According to Dr. Ingelfinger, the number one question for practicing pediatricians is how to treat essential obesity-related hypertension. Dr. Sorof remarked that it may be too ambitious to design a treatment algorithm for the less well defined obesity-related hypertension. It may be more productive to begin with well-defined disease-specific algorithms.

Dr. Falkner made an appeal to begin with the treatment of obesity-related hypertension because of high prevalence and important need to treat. In addition, there is little information on treating this condition. The question then becomes: What is the best design approach for a specific indication? The study design will be affected by the investigators' view of the end result of labeling. Should investigators study a single drug for monotherapy or two drugs in a factorial design? Even if the study design is straightforward, for how long should the study proceed?

The discussion returned to the incorporation of TLC into study designs. In a factorial design, placebo and drug can be randomized and cross-paired with TLC. However, there is a need to standardize TLC across centers. Another approach is to stratify by center. Dr. Rocchini said that "good responders" to treatment show weight loss within 2–3 weeks; blood pressure drops rapidly with weight loss. However, for children who do not respond well to TLC (that is, they do not successfully lose weight), it is difficult to maintain treatment for 8–10 weeks.

Dr. Mattison clarified a point about the design of BPCA studies with FDA. The need for a run-in period is often described. However, the intent is not to be prescriptive in developing a clinical study design, but to allow responders the opportunity to share their ideas and document the evidence for the proposed design. The responders should indicate which components need to be included in the study design.

The meeting participants discussed additional aspects of factorial study designs, including the ability to answer more than one question and assess ranges of dosing. They also discussed concerns about safety with long-term drug therapy and therapy with higher doses. Rare adverse events are also a safety concern and may require a year to allow sufficient assessment. Effectiveness, safety, and expense are important considerations in pediatric clinical trials. These trials may benefit from head-to-head comparisons of drug therapies. For combination therapy, steady state with the first drug must be achieved before the second drug can be added. Pharmacokinetics should be considered across dosing range as well as in study design. A drug's efficacy needs to be established before labeling changes will be considered.

In concluding the open discussion, Dr. Taylor-Zapata asked how many sites would be needed to recruit 300 patients? The progress of several pediatric studies was cited. In one study, there were 33 sites and about 50 percent of the sites were not active and did not recruit any patients; many sites did not even screen for potential study enrollees. Dr. Schreiner said that competing studies should be identified when considering a potential study site. Aspects of patient selection (for

example, obese + hypertensive versus obese + normotensive) and interventions (for example, drug monotherapy, dual drug therapy, drug therapy + TLC) were discussed.

Wrap-Up and Future Directions

Dr. Taylor-Zapata

Dr. Taylor-Zapata thanked the meeting participants for their valuable input. She said the BPCA program staff will discuss the issues raised in this meeting and will consider the information in developing a written request to pediatric hypertension, which will include a suggested clinical trial design. Some leeway in the study design will be given to potential contractors. The initial written request will be sent to major distributors of the drugs to be studied. If the manufacturers decline the written request, drugs will be studied through an NIH-contracted mechanism.

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