CHAPTER 9

CHILDREN AS PARTICIPANTS IN FEEDING STUDIES

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THE NEED FOR STUDIES IN CHILDREN

There are many unanswered questions about the dietary needs of children, specifically regarding nutrient requirements and physiologic responses to dietary components. For example, the Dietary Reference Intakes and other dietary guidelines for children are based on extrapolations and calculations from those established for adults (1–3). Data generated by research on children would be far more suitable for answering these questions. Feeding studies that include children also can lend insight into age-related differences in response to diet; data resulting from such studies are needed to determine the appropriate age for instituting preventive dietary guidance. In addition, studies that enroll not just children but also their close relatives can be useful in clarifying genetic influences on response to diet. (See Chapter 4, ''Genetic Effects in Human Dietary Studies.'')

Enrollment of children in well-controlled feeding studies poses unique challenges to the investigator and to the participating families. Controlled feeding studies can be performed fairly easily during early life when the infant is solely bottle-fed (4, 5). Studies of older children's food consumption are more difficult, however, and typically have relied on one of two primary approaches: either supplying test foods on an ad libitum basis along with recording daily food intake (6–8), or collecting intake data solely through use of dietary records (9). Little has been published about the logistics of conducting feeding studies with children, but it is clear that the biological, psychological, and social factors associated with growth and development will be superimposed on the usual challenges encountered with adult subjects participating in such studies. Investigators thus must be prepared to develop innovative approaches to ensure meeting the scientific needs of the study.

A variety of research settings can be considered in planning feeding studies for children. Occasionally inpatient settings will be appropriate, necessary, and feasible; these offer the highest level of control, but this approach is expensive and not representative of the child's usual environment. Outpatient studies are the more likely option, in which children are provided with their food for consumption on-site or offsite but are otherwise free to pursue their usual schedule and activities. Such studies can also enroll other family members (parents, siblings) if doing so provides an effective means of testing the hypothesis. Residential group settings such as camps and boarding schools also can be considered if the enrollment criteria for the study are relatively broad; such settings would likely provide large numbers of children within specific age and gender groups. Special programs for children with particular health conditions (such as obesity or diabetes) might prove an effective setting for some studies.

The inclusion of children in research studies can be expected to increase in the future. This notion is grounded in a recognition that children have not benefited from many advances in medical research because they have not been included as study participants in a sufficient variety of protocols. Acknowledging this situation, the National Institutes of Health (NIH) recently initiated a new policy requiring that all of its supported research studies involving human subjects consider whether children (in this case, defined as up to 21

eat right. American Dietetic Association

years old) can appropriately be enrolled as study participants (10). Although there will continue to be studies that solely enroll children, it is likely that many investigators will instead be adding children to studies originally designed for adults.

These investigators thus must expect to make child-appropriate adaptations of study designs, protocols, management techniques, and outcome measurements. Researchers also will be called on to provide expanded ethical protections; for example, the informed consent procedures used for adults are not adequate for children, who cannot reasonably be expected to have an adult understanding of the consequences of involvement in research. (More information about this evolving issue can be obtained through the NIH Web site: http:\\www.nih.gov.)

This chapter will present a brief overview of the factors that investigators should consider in designing feeding studies with children. We will draw on our own recent experience as part of the Dietary Effects on Lipoproteins and Thrombogenic Activity (DELTA) program, a multicenter controlled feeding study in adults that examined the effects of dietary fat modifications on plasma lipoproteins and thrombogenic factors. (Also see Chapter 25, ''The Multicenter Approach to Human Feeding Studies.'') The DELTA study diets were whole-food diets with modified total fat and fatty acid composition; the desired nutrient goals were achieved by using specially prepared fat blends and baked goods in addition to other readily available foods (11).

We wished to develop the methodology for enrolling families and their children in controlled feeding protocols at our institution, so we took advantage of the DELTA program to conduct a feasibility study, the Family Feeding Study (FFS) (12). The FFS had a two-part prefeeding phase as well as a feeding phase. The first part of the prefeeding phase of the FFS enrolled 25 children aged 6 years to 10 years, who participated in focus groups to identify food preferences. The results were used to modify the original menus fed to the adult participants in the main protocol of the DELTA study. The second part of the prefeeding phase recruited 60 children aged 6 years to 10 years to do hedonic preference testing of several menu items from the modified DELTA research diets. Finally, in the feeding phase, 6 children from 3 families participated in a controlled diet study comprising two 7-week diet periods separated by one 7-week break.

Behavioral Considerations

Psychosocial Development

According to models developed by Piaget and Erikson (13–15), children progress through five main phases of cognitive and psychosocial development (Table 9-1). These phases affect the act of feeding as well as food selection (16, 17). To be successful, research designs and study protocols must be matched to the children's stage of intellectual, moral, emotional, and social development while meeting nutritional needs. This concept is illustrated in Table 9-1, which shows the linkage between various aspects of feeding studies and Piaget's and Erikson's developmental stages. The table indicates the issues an investigator must consider in designing a protocol appropriate to the age group under study; areas of potential difficulty also are highlighted. If there is flexibility in selecting the age group, investigators can choose which challenges they wish to undertake and which ones they wish to avoid.

As mentioned earlier, in the FFS we chose to work with children aged 6 to 10 years, avoiding the challenges of including preschool-age children and adolescents. However, the youngest child in our study (age 6 years) proved to be the most difficult to work with. Insight into her behavior regarding food preferences and actual food consumption was gained by considering cognitive development theories (see Table 9-1). Although she agreed to adhere to the study diet, she may not truly have understood why she was being asked to consume specific foods. Often, she returned her high-fiber cereal, resulting in a fiber intake well below study goals. A 6-year-old also is likely to separate foods into polarized classes of ''like'' or ''dislike'' and thus may be unwilling to try foods she has classified as ''don't like.'' Once she decided she disliked a food, she was unwilling to try any modification made to that food. Her reluctance limited available study foods.

On the other hand, our 8- to 10-year-old participants were more cooperative. Children at this age begin to think logically, are industrious, and strive for feelings of accomplishment. The older children likely had a firmer understanding of the reasons for participating in the study and consequently had a greater ''need'' to comply.

Although adults can conceptualize beyond personal needs to see the potential good of participation in research, children are essentially egocentric. This means that most decisions about participation and cooperation are generally made through filters of ''me first'' until adolescence is complete (about age 20 years). Consequently, an investigator cannot guarantee consistent dietary adherence through use of verbal reasoning or rationalization. For example, children in a feeding study who do not understand the need to eat every last bit of food on their plates may resist all adult attempts to get them to eat it all. To the children, it is an issue of whether they are in control or whether an adult is telling them what to do.

School-age children, anxious to please the investigator or their parents, may not be truthful about what they did or did not eat. Investigators should recognize that this is not an issue of dishonesty and noncompliance in the adult sense; it is merely a manifestation of the child's stage of moral development. In the child's mind, it may be far better to be dishonest if one gains immediate approval rather than to be honest and receive severe reprimands. Indeed, in our study, despite an apparent strong rapport between investigator and subjects, several children would only reveal consumption of nonstudy foods when their parent was out of the room. This conflict can be disturbing to children. One child, who even-

TABLE 9-1

Developmental Characteristics of Children That Are Pertinent to Feeding Studies

Age Range[1]	Cognitive Stages (Piaget)	Psychological Stages (Erickson)	Physical Considerations
0–2 yr	*Sensorimotor period.* Learning occurs through the interaction of senses and environment, and through manipulation of objects.	*Stage I: Basic trust vs mistrust.* Development of a predominantly unconscious but reasonable trustfulness as far as others are concerned, and a simple sense of trustworthiness as far as oneself is concerned.	Limited motor skills Limited food choices (variety, texture, flavor) Easy to collect urine and feces Difficult to obtain venous blood Rapid growth
1–4 yr	*Preconceptual period.* Classification by a single feature (eg, size). No concern for contradictions. Rapid language development.	*Stage II: Autonomy vs shame and doubt.* Child becomes more dependent and independent at the same time. As the muscle system matures, child has the consequent ability and felt inability to coordinate a number of highly conflicting action patterns. Development of self-control without loss of self-esteem. Recognition of existence as a person.	Erratic appetite (varies with growth and activity) Initiates self-feeding Practices fine-motor skills Food choices limited by texture Increased exposure to potential illness (child care, preschool) Slowed growth rate
3–8 yr	*Intuitive thought period.* Intuitive reasoning based on perception rather than logical inference. Imaginative play.	*Stage III: Initiative vs guilt.* Development of conscience. Advanced language and locomotion permits expansion of imagination, which can lead to fear of what child has dreamed and thought. Child feels guilt for thoughts as well as deeds.	Appetite affected by growth, illness, activity, fatigue Begins to lose teeth Exposure to illness (child care, school)
7–12 yr[2]	*Concrete operations period.* Develops logical cause-and-effect thought. Reasoning becomes rational. Learns to organize, classify, and generalize.	*Stage IV: Mastery and industry vs inferiority.* Child wants to be constructive and wins recognition by producing things and completing work. Industry involves doing things with others. Child can develop sense of inadequacy and inferiority.	Weight gain ~7 lb/yr Prepubertal and pubertal changes begin Fat deposition begins for both boys and girls Rapid growth begins for girls and for some boys Permanent dentition completed
11–20 yr[2]	*Formal operations period.* Comprehension of abstract concepts. Formation of ''ideas''.	*Stage V: Ego identity vs role confusion.* Accrued confidence in one's abilities (ego). Child realizes that his or her own way of mastering experiences is a successful variant of the way others master experience (this often displaces strong previous doubt).	Pubertal changes occur Rapid growth for boys Growth rate slows for girls

[1]Source: Inhelder B, Piaget J (13); Erikson EH (14); Lucas B (15).
[1]Age ranges are approximate. Overlapping age ranges reflect differences in Piaget's and Erickson's definition of developmental stages.
[2]The biological and behavioral changes of preadolescence and adolescence do not occur at the same time, at the same rate, or in the same amount for all children. Thorough individual evaluations must be conducted to determine the developmental stage of each child.

tually terminated participation, sobbed as she revealed consumption of nonstudy candy.

Food Choices: Acceptance and Preference

Two major issues need to be considered before and during the study to ensure children will eat the required food. First, children need to demonstrate acceptance of the foods. Then, investigators must make arrangements so that the child can consume the foods as needed in school and at after-school activities. Investigators usually can adjust the study food to make it more acceptable while still maintaining the required dietary composition. Accommodating environmental and social needs, however, usually leads to the research team having less direct supervision of the participants and less control over the study diet.

Acceptance, which is the degree to which a child likes a particular food (18), differs from *preference,* which is the liking of one food relative to another (19). Children's food choices can be influenced by simply being given the food (''mere exposure''), by the number of times they are served the food (frequency of exposure), by the manner (context) in which food is presented, by the behaviors of family and nonfamily members, and by the environment in which the food is eaten (20–24). Although the taste and texture of many foods are acceptable to children, some foods are preferred to a higher degree than others (Table 9-2). Alternatively, when asked to choose (in a preference test), children may select one food over another while not liking (accepting) either food.

For the most part, each child must be evaluated for his or her own preferences. Parents should not be asked to evaluate the food preferences of their children (25, 26). Even when staff are talking with an individual child, they must take care to distinguish between preference and acceptance. For example, the child may state a preference for pears over peaches but may only accept pears canned in heavy syrup.

Before the study begins, it is important to arrange for each child to taste each of the menu items at least once and preferably several times. This process should include any specialty items produced by the research kitchen (9, 12, 27). Such a step is helpful for several reasons. First, as mentioned earlier, food preferences are specific to the individual and not always predictable. In addition, it may be difficult to describe the items so that children fully understand what each food is and can state whether they will consume the food. Even if every measure is taken to ensure acceptance of study foods, the children's preferences might change as the study progresses. For example, a turkey casserole that was highly acceptable at the start of our study was not accepted at all by the end of the study. Adults are capable of taking a relatively stoic attitude (they ''grin and bear it''); children will eat less of the food or refuse it altogether.

Finally, children are influenced, both positively and negatively, by the likes and dislikes of their peers. This can work to the advantage of the research team, or it can have devastating consequences on their ability to offer variety in the study menu.

It may be unrealistic to expect to develop a lengthy study diet for children in which each participant accepts all foods in prescribed amounts, so that the continual adjustment of foods can be avoided. Therefore, when working with children, researchers should be prepared to adapt menus and recipes on an individual basis. To accomplish this, investigators

TABLE 9-2

Overall Favorite Foods and Favorite Snack Foods of 25 Focus Group Participants 7 Years to 11 Years Old[1]

Favorite Foods	Percentage of Responses
Overall Foods (20 Responses)	
Pizza	40
Spaghetti	10
Macaroni and cheese	10
Mashed potatoes	10
Oodles of Noodles® soup	5
Grilled cheese sandwich	5
Shrimp and rice	5
Baked chicken	5
Tacos	5
Chocolate bars	5
Snack Foods (73 Responses)	
Pizza, all types	26
Granola	16
Fruit	11
Candy	9
Popcorn	8
Potato chips	7
Ice cream	7
Soft pretzels	4
French fries	3
Low-fat granola bars	3
Peanuts	1
Jello®	1
Dry cereal	1

[1]Data from Tilley MA (12).

TABLE 9-3

Adaptation of Adult Menus for Use with Children[1,2,3,4]

	Day 1		Day 2		Day 3	
Meal	**Adult**	**Child**	**Adult**	**Child**	**Adult**	**Child**
Breakfast	Orange juice Three-grain cereal White bread Margarine Jelly Whole milk	Same	Tangerines Raisin Bran® White bread Margarine Skim milk	Same	Orange juice Cheerios® English muffin Margarine Jelly 2% milk	Same
Lunch	Turkey on white bread Mayonnaise Lettuce salad Olive oil Peaches Ginger cookie	Chicken breast on hoagie roll Miracle Whip® Dinner roll Jelly Pineapple Pretzels	Shrimp pasta salad French roll Oatmeal cookie[4]	Turkey on white bread Miracle Whip® Peaches Ginger cookie	Chicken salad White bread Lettuce Tomato Pineapple[4]	Turkey breast on hoagie roll Miracle Whip® Pears Oatmeal cookie
Dinner	Sirloin tips with gravy Corn kernels Lettuce salad with tomato and carrots Dinner roll Butter Applesauce	Same except: No tomato in salad	Chicken jambalaya Spinach salad with green onion French roll Fruit cocktail	Broiled chicken Green beans Lettuce salad (no green onion in salad) French roll Fruit cocktail	Pork chops Spaghetti Green peas Lettuce salad with green pepper and tomato Dinner roll Rolled oat macaroon	Same, except: No tomato in salad[4]
Snack	Snack mix: peanuts, raisins, and pretzels	Same	Pudding Vanilla wafers	Same	Low-fat yogurt	Same

should plan to have at least one researcher and one cook devoted solely to working with the children on a daily basis. In addition, all cooks and kitchen staff must be flexible and the nutrient database must be extremely accurate. Investigators must carefully weigh the advantages of group needs vs individual requests. If allowable, flexibility for some foods should be considered (eg, a peach for a pear) or peanut butter for peanuts. However, if the study requires all children to eat exactly the same foods, once a food is eliminated for one child, it has to be eliminated for all children. This may create tension between individual children and between families while seriously reducing the variety of study foods.

Planning Research Diet Protocols for Children

Beyond the specific research hypothesis, investigators must consider each of the following factors in designing a feeding study protocol for children:

- Safety and ethical considerations
- Nutrient requirements and dietary adequacy
- Physical growth
- Recruitment
- Exclusion criteria
- Screening
- Length of study periods
- Menu and recipe development
- Amounts of food
- Method of monitoring food intake
- Production considerations
- Dining environment
- Incentives and rewards
- Study outcomes, sometimes referred to as endpoint measurements (9, 12, 27)

If the study also includes adults, the menus and recipes may require modification to meet the needs of children (see Table 9-3).

Safety and Ethical Considerations

Investigators must carefully justify any feeding study with children. Research organizations have internal committees, usually termed institutional review boards (IRBs), which are

TABLE 9-3

Continued

	Day 4		Day 5		Day 6	
Meal	**Adult**	**Child**	**Adult**	**Child**	**Adult**	**Child**
Breakfast	Orange juice Bran flakes White bread Margarine Jelly Skim milk	Same	Apple juice Cheerios® English muffin Margarine Jelly 2% milk	Same	Orange juice Corn Flakes® Blueberry muffin Margarine Skim milk	Same except: Blueberry muffin replaced by Applesauce muffin
Lunch	Sliced beef round on onion bun Macaroni salad Peaches[4]	Chicken breast on white bread Lettuce Miracle Whip® Pineapple	Pork stir-fry White rice Rolled oat macaroon	Sliced beef round on onion bun Pretzels Roll Jelly Peaches	Chili Raw carrots Corn chips Dinner roll Jello	Chicken breast on hoagie roll Rolled oat macaroon Carrot sticks Tangerines
Dinner	Turkey almond casserole Green beans Lettuce and tomato salad Dinner roll Ginger cookie	Same except: No tomato in salad[4]	Breaded chicken Pasta with tomato sauce Lettuce and tomato salad Dinner roll Margarine Pears	Same except: Chicken replaced with pork No tomato in salad[4]	Lemon sage chicken Broccoli Dinner roll Margarine Rice pilaf Pineapple	Chili Raw Carrots Broccoli Dinner roll Margarine Rice pilaf Corn chips[4]
Snack	Snack mix: peanuts, raisins, and pretzels	Same	Low-fat yogurt	Same	Brownie	Same

[1]Based on studies with 6-year-old to 10-year-old children as described in Tilley MA (12) and Tilley MA, et al. (27).
[2]The Child Lunch reflects the Adult Lunch from previous day (when foods were made and distributed).
[3]Children were allowed additional snacks by either saving parts of lunch or dinner for later consumption or by eating foods from a preapproved list.
[4]The children disliked eating the composed salads (macaroni salad, shrimp pasta salad, and chicken salad) that were used as vehicles for oils and egg yolk powder in the Adult Lunch menus. Instead the oils and egg yolk from these recipes were added to the Child Dinner menus on the same or following day.

legally mandated to review all research protocols that will enroll human subjects; the research cannot proceed without approval from the IRB. (Also see Chapter 5, ''Ethical Considerations in Dietary Studies.'') Primary concerns are safety and prevention of needless pain and suffering. Investigators must be able to present a thoughtful summary of why the research is necessary, whether the same information could be obtained without inclusion of children, and why inclusion of children is appropriate given the goals of the study.

Parents or legal guardians have the formal responsibility for signing the informed consent documents on behalf of legal minors. These documents should be prepared with the intention of providing the clearest possible explanation of the protocol, its associated risks for the children, and the responsibilities of those who decide to participate. Investigators should also plan to develop informational materials for the children. As mentioned earlier, the younger the children are, the less can they appreciate the consequences of involvement in research. Nevertheless, children who are potential participants deserve to receive an age-appropriate description of the study.

To minimize the likelihood of problems and reassure the IRB, investigators should prepare a written protocol for monitoring safety. This protocol should include procedures for documentation of baseline (prestudy) and during-study data, and also should include ''trigger'' points indicating when it may be appropriate to refer the child to a pediatrician. (It would be prudent to engage the expert advice of a pediatrician during the development of this protocol; a consulting pediatrician experienced in biomedical research might be an appropriate choice as the project medical officer.)

Prominent concerns for children enrolled in research protocols include protection from undue physical or psychological discomfort. In the context of a feeding study, it is relatively easy to imagine the possibility of physical discomfort stemming from hunger (eg, due to delayed mealtimes or a diet with insufficient calories), or from biological sample collection (eg, due to phlebotomy). Many of the potential physical hazards or health risks for children engaged in feeding studies also are predictable and are similar to those faced by adults who participate in such research. Such risks

include those associated with invasive sampling or measuring procedures and allergic reactions to study food (described later).

The possibility of nutritional inadequacy is higher with children because of their higher nutrient density needs. The inadequacy can manifest itself through effects on physical growth and maturation. A thorough description of plans for preventing potential growth problems will help address concerns. For example, to accommodate the expected rate of linear growth during the time frame of the study, investigators must describe their plans for ensuring that the children's needs for energy (and other nutrients) are met, and for evaluating whether the protocol has had any negative impact on growth.

Food allergies and intolerances are common problems with unique implications for feeding studies. Allergies are mediated through the immunologic system; nonallergic intolerances are caused by pharmacologic effects (such as foods with high histamine content) or metabolic factors (such as lactase deficiency) (28). Because both allergy and intolerance can evoke unpleasant or even dangerous symptoms, it is imperative that the screening phase of a feeding study eliminate any person who is likely to react adversely to study foods. The foods most often causing serious allergic reactions are milk, eggs, fish, shellfish, peanuts, tree nuts, soybeans, and wheat, but unexpected cross-reactions with other foods also can occur in susceptible individuals (28). For studies with children, investigators must plan to interview the parent or guardian in detail about any past or current allergies and intolerances; some do not persist as the child matures, but it is advisable to err on the side of caution if there is uncertainty about whether a food sensitivity has resolved. Once the initial screening is over, the parents or guardians of eligible participants should make a final check of all menus for potential high-risk foods.

Psychological constraints imposed by research protocols are less obvious but nevertheless could have undesirable effects on behavior or self-image. Researchers must be thoughtful in anticipating such constraints because they are not well-characterized and will vary among children as well as among studies. Difficulties could arise from protocol features such as strict timing of meals, coercion from adults (parents or research team members) to adhere to the protocol, and social isolation or feelings of being ''different'' from other children (for example, not being able to eat certain foods in settings outside the study). Some children might misconstrue the reason for their enrollment in the study, thinking it is because something is ''wrong'' with them. The possibility of time lost from school, and the consequences of such lost time, should also be considered. Certain behavioral traits, such as extreme shyness or a very slow rate of eating, may make it inappropriate to enroll particular children in a protocol. Researchers should discuss the child's potential behavioral reactions to the protocol with the parents during the recruitment phase.

Nutrient Requirements and Dietary Adequacy

Nutrient requirements for children must be met as carefully as possible throughout the study. There are several sets of guidelines available to assist in planning menus and checking the calculated diets for adequacy of nutrient content. The Dietary Guidelines for Americans (3) suggests the number of daily servings of various food groups that can be expected to provide an adequate intake of most nutrients. The content of specific nutrients, however, should be evaluated by comparison with either the recently published Dietary Reference Intakes (DRI) (1, 29, 30) or the Recommended Dietary Allowances (RDA) (2). The DRI provide recommendations for intake of calcium, phosphorus, magnesium, vitamin D, fluoride, B vitamins, and choline. The RDA provide recommendations for other nutrients, notably energy, protein, and certain minerals (iron, zinc, iodine, and selenium) and vitamins (A, C, E, and K).

Researchers planning diets for individual study participants should note that the DRI and RDA use different age groupings for recommended levels of intake (DRI:

- DRI groups males (M) and females (F) jointly for ages 0 year to 0.5 year, 0.5 year to 1 year, 1 year to 3 years, and 4 years to 8 years.
- DRI groups M and F separately for ages 9 years to 13 years and 14 years to 18 years.
- RDA groups M and F jointly for ages 0 year to 0.5 year, 0.5 year to 1 year, 1 year to 3 years, 4 years to 6 years, and 7 years to 10 years.
- RDA groups M and F separately for ages 11 years to 14 years and 15 years to 18 years.

Energy

Caloric adequacy is the planner's first consideration in designing menus for a feeding study. Basic estimates of energy requirements can be made according to the RDA (2). (Note: As of this time the DRI do not address energy requirements [1].) Recommended levels of energy intake for children are based on the same general algorithms as those described later in this book (see Chapter 17, ''Energy Needs and Weight Maintenance in Controlled Feeding Studies''), but the levels have been adjusted to account for children's higher activity levels (typically 1.7 to 2.0 $\times$ Resting Energy Expenditure) and constantly maturing body composition (2). Expressed on a body weight basis (ie, kcal/kg), energy needs are similar in boys and girls up through age 10 years; during puberty and adolescence, girls' lower activity level and lower percentage of lean muscle mass make their energy needs approximately 10% to 15% lower than those of boys of the same age (2).

The problem of insufficient calories often is easily identified (ie, it is ''self-advertising'') because the child is hungry and says so. (Shy or quiet children may not articulate this

need as clearly). To prevent hunger related to altered mealtimes, flexibly timed snacks can be designed as part of the meal plan. Investigators can reduce the likelihood of insufficient energy intake by providing a slight overage of food through use of unit foods and snacks and allow the child to eat to repletion. Intake is then estimated by measuring the difference between provided food and consumed food. Caloric excess also usually corrects itself within a few days because the children will not eat food they do not need.

Carefully allowing access to food to meet energy needs throughout the study should prevent any negative impact on growth. This can be accomplished by using unit foods specifically designed to both supply energy and to reflect the diet composition being tested. The initial energy levels that are provided for each subject can be determined with the use of 3-day intake records prior to study initiation and validated during the run-in period. Energy levels during the study are manipulated by participants through unlimited access to acceptable unit foods and confirmed by measuring body weight on a continuing and frequent basis throughout the study.

Other Nutrients

The adequacy of protein or micronutrient intake cannot be detected through the immediate symptom of hunger. Menus should be checked for their percent of the recommended intake as either the DRI or RDA (described earlier). The purpose is to guard against deficiencies for all nutrients and to protect against excesses for a smaller number (such as fat-soluble vitamins).

A typical standard for dietary adequacy is that the diet contain 75% of the recommended intake for that nutrient (100% may not be practical or necessary for every nutrient for every day, especially for short-term studies) (31). It then is possible to calculate each child's likely range of intake and requirement of calories and nutrients; examine the resulting data on the basis of either nutrient density (units nutrient/1,000 kcal) or absolute daily intake; and then evaluate intake against the recommended level (DRI or RDA) expressed in the same units. Physical activity level should be considered in this assessment. Depending on the protocol, it also may be appropriate to monitor for adequacy of protein, vitamin, and mineral status using biochemical markers, provided the protocol permits collection of the needed biological samples.

Physical Growth and Anthropometric Data

Growth Charts

Protocols collecting anthropometric data on children, either as primary endpoints or to monitor safety, should be designed in keeping with published standards for making the measurements and evaluating the results (32). In the United States, these are provided to the public by the National Center for Health Statistics, an agency of the US Public Health Service (Hyattsville, Md) (Web site http://www.cdc.gov/nchswww). The basic descriptive data have been available for many years in the convenient form of charts that enable measurements for height, weight, weight for height, and head circumference to be graphed against age- and gender-specific population-based percentiles (5th, 10th, 25th, 50th, 75th, 90th, and 95th) ''bands'' (33).

A new set of NCHS growth charts, available in early 1999, represents the first revision of these important data in over 20 years (34, 35). These charts are based on data pooled from five national surveys conducted between 1963 and 1994 (the first, second, and third National Health and Nutrition Examination Surveys and the second and third National Health Examination Surveys). Two sets of charts provide gender- and age-specific percentile distributions for infants (0 months to 35 months, inclusive) and children (2 years to 19 years, inclusive) for weight, stature, and body mass index (replacing the older weight-for-height measurement); the infant charts also provide head circumference percentiles. The charts represent population-based values for the entire US population, with all ethnic/race groups combined, and will have an expanded set of percentile bands: 3, 5, 10, 25, 50, 75, 90, 95, and 97. (The new growth charts, and information about their use, will be made available at the NCHS Web site: http://www.cdc.gov/nchswww.)

Alternatives to the NCHS growth charts occasionally are needed for some protocols. Some investigators may wish to use race-specific standards (36, 37), although the need for this is a matter of debate. Descriptive data are also available for other measurements, such as skinfold thickness, waist-neck length, and limb circumference (37–41).

Collecting and Evaluating Growth Data during Feeding Protocols

As for any other study measurements, the principles of valid research technique apply to anthropometric data and other means of assessing growth and development. The investigator's ability to detect problems with growth thus requires that sources of variability in these measurements be controlled as much as possible. It is critical that the procotol include procedures for standardizing aspects of data collection such as the measuring devices, participant management procedures (eg, type of clothing worn or time of day measurement is made), and techniques for recording data.

Healthy children gain weight and height over time until they reach full adult size. They may go through periods of stable height and weight, then grow quickly in a ''spurt.'' Weight also fluctuates because of erratic physical activity levels. Some of these fluctuations also reflect measurement errors (on the part of the person making the measurement or in the measuring device) and other inconsistencies (such as differences in shoes or clothing, or whether a meal was recently eaten).

In particular, studies assessing height as an endpoint or as a safety marker must consider that height measurements

are sensitive to error because of the effect of small changes in child's stance and posture (or body position for prone measurements of infants).

In the context of feeding studies, growth usually is assessed by measuring height and weight. Head circumference also is typically measured in infants (< 3 years). Occasionally skinfold thickness measurements are needed to evaluate changes in adipose tissue content. Studies involving infants may wish to consider assessing developmental stage according to a standard scale such as the Denver Developmental Screening Test (42). Some long-term studies of adolescents may find it pertinent to assess Tanner stages of sexual maturation (although this scale requires a physical examination and highly personal questions that may be considered intrusive) (43).

Concerns about growth focus on three main areas: the possibility of delayed or reduced growth in height and/or weight; the potential for induction of overweight or obesity; and the chance of delayed or accelerated maturation. Some studies might find it necessary to assess body composition in order to evaluate the nature of observed weight gain or weight loss; that is, they might identify which body compartment is gaining or losing such components as water (ie, there is a possibility of dehydration), muscle, or adipose tissue.

The potential for growth problems is greater for certain study designs. Diets that are high in bulk, have very high or low caloric density, or require unpalatable foods can distort the normal regulation of energy intake. Long-term studies (of several months or longer) must institute more stringent monitoring procedures. Finally, studies enrolling children during rapid growth phases (infants or adolescents) must be alert to potential effects on growth velocity. Written protocols for feeding studies with children should include reference values and cutoff points above or below which further evaluation will occur.

There are no hard-and-fast rules for the frequency of making anthropometric measurements during a growth study with children. The frequency of measurements should be based on the data needs of the protocol, the practicalities of coordinating data collection with other study activities, and the expected rate of growth during the time frame of the study. However, frequent measurements can help establish a predictable routine, which can in turn foster adherence to the protocol. Frequent measurements also provide a means of reassuring the parent or guardian that the child's well-being is safeguarded.

Measurements are made at baseline (before the study begins), periodically throughout the study, and then at the end of the data collection period. Again, it is important to ensure that uniform methodology is used at each time point. Baseline data preferably include several repeated measurements, made approximately 1 week apart. This provides information on within-child variance. Historical data from family or pediatrician's records can also be helpful in characterizing long-term growth patterns that are typical for an individual child.

During the course of the study, unless the protocol requires growth data as endpoints, suggested approximate time frames for monitoring and adherence are: weight 1 or more times each week; height 1 or more times each month. The advice of a statistician should be sought in determining the optimal schedule for anthropometric measurements. For example, an 8- to 9-year-old child gains about 8 lb a year. In a 3-month feeding study, weight should be measured often enough to reliably detect a 2-lb gain (approximately once or twice a month), but investigators might establish a routine for adherence and measurement weight 1 to 3 times a week.

After the data are collected, appropriate descriptive statistics should be generated. The age- and sex-specific percentile value should be determined for each child. In addition, the mean, median, range, and so on of age- and sex-specific percentiles should be calculated for the entire study cohort and for the children assigned to each treatment group.

Growth data also must be analyzed with appropriate statistical techniques. In general, data for the treatment group are analyzed for evaluating study outcomes, and data for the individual are analyzed for monitoring safety. Data can be analyzed as continuous variables (actual measurement results) or as categorical variables (specific percentiles or percentile bands). Data analyses for small studies ($n < 20$) probably will need to use nonparametric statistical methods. Evaluation of data collected at different time points requires appropriate paired or other repeated measures techniques.

Software packages for graphing data on standard charts provide a convenient means of tracking the growth of individual children and of treatment groups overall (44); also consult the NCHS Web site (http://www.cdc.gov/nchswww). For individual children, it is unlikely that changes will be observed in percentile rankings between successive measurements; short-term alterations of less than 10% to 25% in percentile rank may not be meaningful unless accompanied by other problems. For groups of children, the average percentiles likely will be consistent if all is well.

For some data analyses, it may be necessary to statistically adjust for the height (or weight, or other anthropometric measurements) of the child's biological parents. The adjustment would be made by using the parents' data as a covariate in multiple regression or other analytical procedures. The measurements (which are preferably made directly by the investigators rather than by self-report) can either be used as continuous variables (such as height in inches or centimeters), or they can be collapsed into categorical variables based on population percentiles (such as 25th percentile for height for adults).

Food Intake and Appetite

A critical decision concerns the amount of food served to each child. Controlled feeding studies, by definition, require the ingestion of all study foods presented, with flexibility in adding unit foods to accommodate energy needs. Investigators have two primary ways for defining the amount of

food that the subjects eat. The first approach is to insist that the entire amount of premeasured food is eaten daily with adjustments made to maintain a stable weight. This technique can be used with young infants or adults, but in our opinion it is not suitable for children. For children of most ages, the most realistic approach (albeit less accurate) is to serve an excess amount of all foods, allow ad lib eating, and calculate portions eaten by difference. It accommodates growth spurts and illnesses that can undermine carefully calculated energy determinations and eliminates potential conflicts.

Whereas a primary issue with physical development is erratic appetites resulting from fluctuating energy needs, a primary issue in the child's psychosocial development is control. As stated previously, during certain stages of development, children have a strong need to exert control over their environment. Refusal to eat some or all of a particular food may be an expression of that need. Investigators must balance these equally important and often divergent concerns prior to determining how much food should be offered.

In addition, investigators must be flexible in adjusting energy needs. On any given day, the child may not want all the food provided or conversely may want more. Use of free-choice foods, such as diet carbonated beverages or fat-free/sugar-free gelatin desserts, should be considered along with provision of unit foods. If free foods are acceptable, investigators should design the study to allow a range of nutrient intakes, rather than a single target figure. In reality, this may be the only practical study design. Another possibility is to work with a mean weekly goal rather than a daily, or even meal-by-meal, target. This built-in flexibility may serve to diminish the anxieties of both investigators and families as well as to facilitate compliance.

Investigators must be pragmatic about the degree to which they can influence children's appetites. The tools available for addressing this issue are well known to experienced parents: encourage physical activity as appropriate and space the snacks and meals at sufficient intervals to allow hunger to develop. These techniques must of course be applied with discretion and without unduly coercing the child.

Rate of growth, physical activity, amount of sleep, stress, and illness all significantly affect a child's appetite (17). Even the loss of a tooth during the study influences subsequent intake. However, investigators should recognize that for any one child, although energy intakes for each meal can vary greatly from day to day, over a week's time energy intake remains fairly constant (6, 9). In addition, there may be tremendous differences in energy intakes between study subjects of the same age (6). It is imperative for the investigator to maintain close daily contact with each child and not rely solely on anthropometric and dietary intake measurements to monitor physical status.

Time Factors

Studies with children likely will require a longer run-in period than studies involving adults. A longer acclimation period allows researchers to carefully scrutinize subjects and their families to determine their compliance and provides sufficient time for menu and recipe adjustments. The actual experimental feeding periods can proceed for the normal length of time. However, if the experimental period is too short, adequate adjustments and a stabilized regime will not have been established. If the study continues for too long a period, boredom, sudden growth spurts, and noncompliance issues may occur.

Another consideration is to determine how many different diets are actually necessary for the study. Children are more comfortable in a routine. Thus, the fewer dietary changes, the more likely the children will cooperate.

Arrangements for birthdays, holidays, and special events should be planned prior to the study. For example, if Halloween occurs during one of the feeding cycles, it is close to impossible for the children not to eat any candy. Therefore, investigators must work with the families to incorporate a favorite candy into the study menus.

Researchers working with school-age children also must accommodate school and after-school needs. To avoid interfering with these activities, studies can be undertaken in the summer. However, many families are unavailable for long-term studies during this period. We found the children enjoyed carrying study foods to school in customized lunch boxes. During the school year, special arrangements must be made for birthday parties, sports events, and holiday celebrations to ensure the study children will not feel different from their peers. Some teachers willingly accommodate study protocols, whereas others believe it is not their role.

If possible, the study diet should include a variety of free-choice foods, in addition to unit foods, that study children can enjoy within the context of the feeding protocol. If children do ingest foods outside the scope of the study, it is extremely important for investigators to be able to account for these selections and to adjust the experimental diet accordingly so that nutrient goals are met.

Collecting Biological Samples

The endpoint measurements needed to test the research question may influence which age group is selected for study. Ultimately, investigators must ask which measures would be preferable to have and which are absolutely critical. Young children may be terrified of venous blood draws but may accept the more familiar finger prick. Conversely, school age children may have the reverse reaction. Venous blood draws may be acceptable on a monthly basis but not on a weekly basis. The volume of blood collected at any one time, and throughout the study, is contingent on the child's weight and body size. Thus, the younger the child, the less frequent the blood draws and the smaller the collected volume. Acclimating children to the collection procedure and using friendly adults dressed in conventional clothing (ie, no laboratory coats or surgical scrub clothes) may facilitate acceptance of blood draws.

Although they may tolerate an initial blood draw, children may change their minds and not cooperate in subsequent collections. As stated, we experienced this situation with a 6-year-old who had to be dropped from the study after participating for 7 weeks. Therefore, our experience suggests that investigators should anticipate a higher termination rate with children than with adult subjects.

Urine collection protocols also must be appropriate to the age of the participants. Spot urine collections might be more feasible for children who attend school. A 24-hour collection might be better suited for weekends and for preschool-age children who have been toilet trained. Collection of feces and urine is easier with older adolescents.

Some biological samples can be collected with minimal physical burden, pain, or risk. These include hair and nails (for trace element studies) and buccal swabs (for genetic analyses). Even so, some children object strenuously to having their nails or hair trimmed, some parents may be concerned about cosmetic aspects of sample collection, and some infants may not have long enough hair or nails to yield an adequate specimen.

Study Management

Recruitment and Screening

Establishing early contacts with recruitment sources is essential. Well before the study begins, investigators should develop relationships with local pediatricians and family practice physicians. This can facilitate securing participating families as well as obtaining informed consent through the IRB because many physicians sit on these boards. For example, we contacted our area's primary pediatric practice 12 months prior to initiation of our projects. The pediatric staff distributed a questionnaire to patients' families. From these questionnaires we were able to gather information on: the level of interest in participation (both in taste tests and in the actual studies); existence of food allergies and intolerances that would preclude inclusion of specific families; the ages of children likely to receive parental permission to participate in a feeding study; the types of foods routinely served to children in our area; and issues of outcome measurements (particularly blood draws). This preliminary information proved invaluable as we established study protocol and design.

Recruiters should include an interview with the child and each family member privately, along with a family group interview. Family dynamics should be carefully observed. An ideal way to incorporate this idea into the study protocol is to gather food intake information using individual and group interviews of the study child(ren) and the parent(s). Following the interviews, evaluation of responses regarding acceptance and preference of critical food items can be made. In addition, information regarding the feeding environment (eg, how families handle mealtime behavior or the offering of desserts) can be obtained. If the recruiter senses any problem at this stage of the study, careful consideration should be given to excluding the family. It is far less expensive and detrimental to the study to exclude the family at this point than to have them terminate participation later.

Intensive screening is required, especially if the study will include all other family members. In our experience, to ensure continual participation by the study children, parents and other siblings should be included in all activities of the feeding study even if these family members do not meet study criteria. The increased costs are offset by savings generated in maintaining subjects in the study. Careful consideration should be given if recruiters sense any ambivalence on the part of either the children or the adults about issues such as food likes and dislikes and endpoint measurements (particularly blood draws). Children older than age 8 should be provided with the same detailed description of the study as the adults, should be given an opportunity to ask questions, and should sign the informed consent form along with the parents. In the case of children who live with a guardian or a single head of household, attempts also should be made to obtain the approval of the nonresidential parent (when feasible and appropriate).

Potential subjects should not be included in the study if they seem to change their minds about accepting crucial food items, if there is resistance to working within the group decision-making process, or if parents keep requesting changes on behalf of their children. A key reason for exclusion is the suspected or proven existence of food allergies or sensitivities that might limit consumption of specific foods or entire food groups. Allergies are commonly found to dairy products, wheat, nuts, peanuts, fish, shellfish, and corn; lactose intolerance is prevalent among many ethnic groups. A note signed by the child's doctor should clarify the presence or absence of food reactions.

Children and their families should be offered incentives to participate. Although monetary incentives are generally given to feeding study participants, parents may not agree to such incentives being given directly to their child. In this case, the parent may receive the monetary compensation or a savings bond may be purchased in the child's name. Whether or not money is given directly to the children, additional incentives are required to maintain interest. Facilitated group discussions should be used to tailor incentives to families. For example, although young children might like some identification with the ''special'' study, school-aged children might not want that recognition. Suggestions for study incentives include gift certificates to book or toy stores; passes to movie, bowling, or miniature golf establishments; ''field trips'' to an arcade; and trinkets served with meals (such as rubber spiders for Halloween).

A note of caution: Some parents may use incentives (especially monetary ones) as a threat over their child to control compliance. If the investigator becomes aware of this behavior, the issue should be addressed immediately. Indeed, one child was dropped from our study because she was terrified of the blood draws. She did have the first draws done;

however, on one occasion, the investigator overheard the mother coercing the child to cooperate. The mother had promised the child a new color television if she participated and threatened to withhold this reward if the girl did not permit blood collection. We compensated the family for the child's participation but excluded her from continuing with the study.

Mealtimes in the Research Setting

The dining environment should be designed to appeal to children and foster their involvement with the study. In our dining room, tables were arranged to encourage family interaction. We found, however, that the families came in for dinner at different times because of personal schedules, which limited the between-family interaction we had anticipated. We used coloring books, jigsaw puzzles, games, and selected videotapes to entertain the children prior to and after meals and clinical procedures.

All in all, most of the young subjects got along well enough for the entire dining environment to be congenial, even for those adults participating in a concurrent study. This is an important observation when meals are being provided for spouses and children of participants in an adult feeding study. Nevertheless, not all children developed close friendships during these times. In fact, to our dismay, we found the words ''I hate (*name of person*)'' written in a coloring book. We believe it was written by a subject who complained that another child was ruining the books by drawing a mark on each page without coloring.

The physical arrangements of the research kitchen and the dining room also may require adaptations. Such remodeling includes appropriate furniture (high chairs, booster seats), feeding utensils (sipper cups, small plates, and implements) and play space with toys; child care supervision; and safety precautions (eg, blocked access to kitchen, rounded table edges, covered electrical outlets, placement of hot food and equipment out of harm's way). In addition, sufficient storage and refrigeration space must be available in order for the study to accommodate individual food requests. If food intake is to be assessed by weighing, leftovers may need to be stored for weighing at more convenient times, requiring additional refrigerator and/or freezer space.

The mealtime behavior of families and children can be complicated. Once study subjects have been selected, the staff and parents must develop discipline techniques acceptable to each family. Although we did not encounter any problems, there may be occasions when staff feel it necessary to convey to the child that a particular behavior is disruptive. Some families will be comfortable with the use of relatively stern tones of voice; others may consider this too severe. If parents feel their child is being treated harshly or unfairly, or think the child is being criticized, they may withdraw from the study.

Besides discipline techniques, feeding strategies should be established. In our study, one parent preferred milk to be served to her daughter following, not during, the meal; this was easily accommodated. Toward the end of the study, a 10-year-old boy began to return his leftover food from lunch squashed. The investigator, rather than confronting him about his obvious displeasure, decided to spend more time with him. He revealed his perception that the investigator was ignoring his needs. The child returned to his normal, cooperative demeanor once the investigator acknowledged him in this way.

Enhancing Compliance

Ensuring intake of the study food requires constant adaptation, and table manners may suffer as a result. In our study, we needed to find ways to incorporate specific oils into daily intake. The menus originally designed for adult participants delivered important dietary fats (oils and egg yolk powder) in the form of baked goods, casseroles, salad dressings, and composed pasta and meat or fish salads. Occasionally a layer of oil would rise to the surface of the food or would settle on the bottom of the serving dish. The adults were willing to drink the extra oil directly from the dish, but we could not depend on the children to do this. Initially, we tried using oils as salad dressings but we quickly found out the children would not always eat salad. We resorted to having the children ''mop'' up most of the oil with their rolls, although some had been taught not to do this at home.

Many decisions concerning variety and plate presentation are dependent on the kitchen staff. Some staff members enjoy accommodating children's needs and will work with the families. They are willing, for example, to use divided plates to make sure the meat does not touch the potatoes, if that is what the child wishes. Other staff complain about these requests and may not be well suited to work on these projects.

Monitoring food intake is a major issue when food is eaten off-site. It is always difficult for subjects to maintain a balance between encouragement to eat only study foods and honesty in reporting consumption of nonstudy foods. This problem is only enhanced when children are involved. Because detailed records are critical during the data analysis phase, daily recording of food intake should be encouraged. However, daily record keeping by children may be impossible, or at best, inaccurate. Children may not read or write well enough to complete even the simplest form and their oral recall may be unreliable, especially if describing food consumption when a parent is present. Parental recall is not recommended, especially if the parent is not present at every eating occasion. We suggest that children should be interviewed, away from their parent, to increase positive interaction between the investigator and the child and to enhance accuracy. Logs or checklists also can facilitate recalls. Accurately monitoring food intake may be more difficult, however, especially for infants who are breast-fed, have begun to explore their environment with their mouth, or have started self-feeding.

It is also imperative for investigators to be aware of any medications the child is taking on a continuous or sporadic basis both before and during the study. Medications can affect many factors relevant to feeding study protocols, including the biological response to the dietary intervention and the taste of the study food. In addition, medications may represent an uncontrolled source of nutrient intake for target nutrients; children's preparations often are compounded in sweet sugar- and alcohol-containing syrups that can contribute calories to the diet (45). The possible contribution of medications to nutrient intake should be evaluated carefully for protocols requiring stringent dietary control.

An alternative way to improve intake accuracy (albeit tedious, labor-intensive, time-consuming, and expensive) is to weigh foods prior to and after eating. However, children often mix foods together on the plate, making it almost impossible to accurately weigh individual food items (especially oils and table spreads).

Throughout the study, investigators must plan to assess behavior that might be linked to problems with dietary protocol. These can be related to a range of issues, such as hunger from insufficient caloric intake, frustration with unsatisfactory timing of meals, and loss of control over food choice. Behavioral problems impinging on the study can range from lack of energy or interest, sleepiness, tantrums, crankiness, somatic complaints such as stomachache or headache, oppositional behavior, and general malaise.

It is valuable to consider in advance what information would be useful and to devise a plan for collecting it in a systematic fashion. Quantitative information is preferable (how many times last week did child do X, or how often did Y happen?), because it lends itself to comparisons of baseline and during-study results, and the chance of evaluation bias is lower (although seldom eliminated). It might be necessary to refer the family for counseling or to drop the child from the study. However, given the high investment of personnel and resources that each participant represents, it is far better for investigators to develop options that would support retention in the project.

Although it may be impossible to eliminate all problems, we found daily contact between a single researcher and all family members was essential in dealing with these feeding issues. This investigator must be diligent in note taking so that, over the course of the study, a written record is carefully maintained. Building close rapport and trust is essential in working with children. Compliance may be compromised when protocols allow consumption of study foods to occur outside the research environment, but a close rapport can facilitate honest and open disclosures by children of ingestion of nonstudy foods and even of accurate dietary recalls of study foods.

Conclusion: Adapting Research Diet Protocols for Children

Investigators must be cognizant of the wide range of physical and psychosocial behaviors inherent to a feeding study involving children. Compromises are necessary to accommodate inclusion of children. Studies enrolling children as well as adults must expect to adapt the diets to fit the needs of both groups. Children in late adolescence often are willing to eat "adult food," but enrolling preadolescent and younger children likely will require many modifications to the original menu plans. Newly instituted requirements for children's inclusion in federally supported biomedical research will make this exercise a common experience for investigators.

Excessive adjustments to protocol may cause final nutrient intake to differ greatly from study goals, but inflexibility in adapting the protocol may led to increased noncompliance and attrition. For this reason, we strongly suggest investigators use a range of acceptable nutrient values (eg, 28% to 32% energy from fat rather than an exact 30%) or determine an acceptable difference between diet treatments (eg, 5 g difference in fiber intake). Rather than expecting a child to comply with a specific level of intake on a daily basis, it is more realistic to expect and accept a defined level of flexibility in nutrient intake over time. Another approach would be to plan a more extensive set of menus, using food substitution lists and even parallel meals and menus, so that the study goals can be met by offering the child a wider choice of foods having equivalent nutrient content.

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