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Perspectives from the symposium, The Role of Nutrition in Infant and Toddler Brain and Behavioral Development

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Abstract

This symposium examined current trends in neuroscience and developmental psychology as they apply to assessing the effects of nutrients on brain and behavioral development of 0-6 year olds. Although the spectrum of nutrients with brain effects has not changed much in the last 25 years, there has been an explosion in new knowledge about the genetics, structure, and function of the brain. This has helped to link brain mechanistic pathway by which these nutrients act with cognitive functions. Clear examples of this are linking of brain structural changes due to hypoglycemia vs. hyperglycemia with cognitive functions by using Magnetic Resonance Imaging (MRI) to assess changes in brain-region volumes in combination with cognitive test of intelligence, memory and processing speed. Another example is the use of Event Related Potential (ERP) studies to show that infants of diabetic mothers have impairments in memory from birth through 8 months of age that are consistent with alterations in mechanistic pathways of memory observed in animal models of perinatal iron deficiency. However, gaps remain in the understanding of how nutrients and neurotrophic factors interact with each other in optimizing brain development and function.

Keywords

Brain; behavior; event related potentials; magnetic resonance imaging; nutrition; nutrients

Institutions and objectives of the symposium

The Department of Nutrition at the School of Public Health of the University of North Carolina, and Mead Johnson Nutritionals hosted and sponsored a two-day symposium on emerging nutritional issues in brain development and cognition. This symposium series is part of a collaborative research-program agreement between these two institutions that aims at enhancing innovation through science based on infant and childhood nutrition.

The goal of this two-day symposium was to bring together researchers from a diverse set of academic fields (e.g., developmental biology, nutritional biochemistry, cognitive and developmental psychology, brain imaging and cognitive science) and industry to survey the state of the art, and to identify unanswered research questions in the area of nutrition, brain and behavioral development in children 0-6 year olds. During the last decade, the use of neuroscience-based technologies like event-related potential (ERP) and functional magnetic

resonance imaging (fMRI) by developmental psychologists has advanced our understanding

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of how the nervous system controls behavior. Concomitantly the integration of a multidisciplinary approach in neuroscience has seen an emergence of new knowledge in understanding the mechanisms of brain development and cognition (1). This symposium provided an opportunity to assess the implications from these advances in identifying new trends in the role of nutrition in brain development and function. The availability of quantitative methods for studying all aspects of neural structure and function from its genetic determination to expression in human behavior should have an impact in our understanding of how nutrients and nutritional intervention can enhance mental development.

The symposium included a keynote address that was followed by two workshops: The keynote speaker was M. Georgieff, who presented an overview of the role of nutrition in brain development during the infant and toddler years. He emphasized the general principle that nutrients are more or less essential for normal neural cell growth and development depending on the timing of a nutrient delivery in relation to the critical period of neurogenesis and synaptogenesis (2,3).

The first workshop addressed the use and interpretation of mechanistic models in assessing the role of nutrients in brain development and function, focusing on trace metals by C. Levenson (4), docosoahexanoic acid (DHA) by L. Broadhurst (5), choline by C. Williams (6) and glucose by T. Hershey (7,8). This workshop examined the evidence supporting the effects of nutrients on neuroanatomy, neurochemistry and functional outcomes *in vitro* or in animal models, and in the case of DHA in ecologically different populations. The second workshop addressed assessment technologies and their applications to measuring neuronal and behavioral variables in children, including measures of cognition like working memory by J. S. Reznick (9), attention by J. Colombo (10), brain activity measures like ERP by K. Thomas (11) and MRI by K. Botteron (12). Tables 1 and 2 list the themes and presentation-topics at each of the workshops and the set of directives that presenters used to develop their presentations. We report here on the perspectives generated from these directives and the salient questions posed during the workshops.

Role of nutrition in brain development and performance: General principles

The brain has specific nutritional requirements and limitations. For example, the brain is geared to use glucose as its main source of energy, and it does not have the capacity to build stores of fat or glycogen as do other organs. From this perspective, the brain is a costly organ to maintain, and it functions at the expense of other organs (13). Moreover, the brain has specialized tissue in which functionality depends upon the buildup of electrical potentials and their conductivity through long cell-bodies and synaptic gaps between these cell-bodies. This dependence is reflected in a higher need for special fats such as gangliosides, sphingolipids, DHA. and for divalent cat-ions like Ca++. The central nervous system is contained in a highly protected environment through the blood-brain barrier that blocks the passage of some substances from the blood stream while allowing others to pass that are essential for the brain's metabolic function. This results in the selective transport of substances based on their physicochemical properties.

Nutrition is the sum of all processes involved from the acquisition and ingestion of food and water through their digestion and assembly into metabolically functional substances (i.e., nutrients) for energy, growth/development, tissue repair and replacement, or elaboration of products (e.g., human milk). Thus, a complex sequence of events precedes any measurable nutrient-related outcome. Moreover, the systemic distribution of these nutrients and their utilization by organs and organ systems within the body are under homeostatic control that drives a state of metabolic sufficiency (i.e., increasing nutrient intake does not necessarily enhance function, and excess nutrients can be stored, excreted or degraded). The functional

needs for these nutrients are not selective or organ specific, and nutrients are not hormone-like (i.e., exert control and regulate the activity of certain cells or organs), except for vitamins A and D. Although nutrients follow pharmacokinetics principles such as absorption, distribution, and clearance, they are not drugs in the sense of dosing, administration and tissue-specific action.

Taking all of the above into consideration, some general principles of brain nutrition have been proposed (3,14), which we have expanded herein: i. all nutrients are necessary for prenatal and post-natal brain development and function; however, there are some nutrients that have specific critical roles in brain nutrition (e.g., vitamin A, DHA, iodine, iron, zinc, choline); ii. the brain effects of these particular nutrients are intrinsically related to their physicochemical characteristics (e.g., metals like iron, zinc and iodine are enzyme components, fatty acids like DHA are a membrane component) and thus, nutritional effects can be quite specific. For example, iron deficiency may affect the synthesis of neurotransmitters while DHA deficiency affects their release; iii. the essential roles of nutrients are time and dose dependent (e.g., periconceptional supplementation with vitamin A is teratogenic, whereas immediately postnatal, it is beneficial); iv. the efficacy of nutrients is regulated within a narrow and tissue-specific range (e.g., iron, vitamin A), and v. nutrients that have essential roles in brain development and function have specialized transport mechanisms that carry them across the blood brain barrier (e.g., vitamin A and retinol-binding protein), or their physicochemical characteristics allows them to readily cross the blood brain barrier (e.g., short-chain vs. long chain fatty acids).

Causal inferences regarding the effects of nutrients on brain development and function

The crucial question of causality is complex because evidence for causality requires more than just a statistical association between nutrient deficiency and impaired brain function or problematic behavior especially in human studies. This has been discussed extensively in previous publications (15,16). In experimental animal models, the plausibility of a nutrient effect has been supported by linking nutrient deficiency to structural and/or biochemical alterations in maturation that are themselves accompanied by functional changes (e.g., neurological sequelea of fetal iron deficiency) (2). In human studies, it is difficult to demonstrate these pathways because this would require the use of invasive procedures. However, new technological advances in neuroscience and psychological development offer a promising possibility of using non-invasive procedures to assess the association between mechanistic pathways and behavioral changes.

Critical periods vs. windows of opportunity in determining the essentiality of nutrients in prenatal and postnatal brain development

A critical period typically encompasses a very narrow time-frame during which a particular brain region develops or in which a specific experience must occur (17). In this regard, postnatal periods are relative broad in function and thus, effects of nutrients on brain and behavioral are difficult to define and detect. Additionally, changes in nutrient supply may occur and affect brain development at multiple time points across these periods. For example, iron deficiency may affect brain development and function in early infancy, during the toddler years and in adolescence (3). Thus, in essence, these periods should be viewed as “windows of exposure or windows of opportunity” upon which nutrients may exert an effect, rather than critical periods as in prenatal brain development (17).

Defining normal brain development during childhood

To demonstrate the effects of nutrients on brain development and behavior during infancy and childhood, an important first step is to define normal brain growth and to establish windows of possible nutrient effects based on neurophysiology and behavioral changes. However, there is limited normative data on brain development and on specific milestones, especially during the toddler years. The National Institutes of Health MRI study of healthy brain development offers an opportunity to obtained reliable data on brain growth from a healthy cohort of infants and children (18).

The following section addresses the salient questions and answers from the workshops: Question 1: How applicable are reported findings on structural brain volume changes observed in youth with Type I diabetes to non-diabetic populations, as the non-diabetic children may experience marked swings in blood glucose due to high glycemic diets? **A:** Brain-related findings from youth with Type I diabetes are not easily generalized. These individual had severe hypoglycemia (i.e., history of seizures, loss of consciousness or inability to arise from sleep), whereas those with hyperglycemia had blood glucose levels observed that were extreme values (i.e., blood glucose concentrations of 400 mg/dl, or hemoglobin A1c of 12) (7). These extreme blood glucose levels are not encountered in normal populations. [postscript] The observed changes affected the structural integrity of the brain, although they were not significantly different when compared to non-diabetic siblings in regional grey or white matter volumes (7). Within the diabetic group, however, individuals with one or more severe hypoglycemic episodes showed smaller grey matter volume at the left temporal-occipital region, whereas individuals with episodes of severe hyperglycemia showed smaller grey matter volume in the posterior cortical area (7). These structures are associated with brain performance related to episodic memory system and higher-order visuospatial function. In a subsequent study of a similar population, the authors assessed the effects of severe episode of hypoglycemia vs. hyperglycemia on cognitive development (8). Frequent severe hypoglycemia was associated with decreased delayed recall of explicitly learned information, whereas severe hyperglycemia decreased delayed recall of explicitly learned information and spatial analysis skill (8). These studies are important because they link brain structural changes with cognitive functions by using MRI studies of brain region volume in combination with cognitive test of intelligence, memory and processing speed (7,8)

Question 2: In which area of the brain does the metabolism of glucose occur and can it be identified using MRI imaging? **A.** It is important to recognize that the main source of energy for the brain is glucose and thus, it is not surprising that activity in some specific regions in the brain is detected with MRI scanning. The temporal/occipital cortex shows very high baseline glucose metabolic rates along with other regions like the left superior temporal and the angular gyri (7 and references within). Another area of the brain that should be considered is the hippocampus, which is critically involved in certain forms of learning and memory, but, paradoxically, is one of the most vulnerable regions of the brain to hypoxia/ischemia. Additionally, through these presentations we have learned that the hippocampus is “metabolically needy” as several micronutrient and macronutrient deficiencies affect this region. In this regard, it is important to note that segmentation and volumetric evaluations of the hippocampus can be accomplished with high resolution MRI (19).

Question 3: Is it possible to manipulate neurogenesis with interventions using different micronutrients like zinc, iron or choline or their combination to reverse the noxious effects on the brain caused by toxic agents that work at different levels than do these micronutrients? **A.** Although neurogenesis contributes to plasticity, the micronutrients that have effects on stem cell differentiation may not be the only regulators of this plasticity. For example, pre-natal supplementation with choline creates growth factors concentrations that enhance the

generation of synaptic connections. Thus, it is not only neurogenesis but also synaptogensis that ameliorates the effects of injury. Indeed, the coordination through growth factors and nutrients may explain why these effects are not specific but rather general and thus, this micronutrient intervention mitigates but does not cure the damage done by the toxic agents. It is conceivable that micronutrients may provide the right environment for neurogenesis and synaptogenesis to take place where it may be necessary, but neurotrophic factors provide the start-up signal.

Question 4: Studies on the mechanisms by which nutrients affect brain development and performance are often conducted using animal models. Does this represent a problem when inferences on nutrient levels and their extrapolation to human populations are based on results from comparing control vs. deficient or supplemented diets in these animal studies? **A.** First, it is important to realize that the rat and other animal species develop and mature at varying rates from humans, and that this difference has important implications for extrapolation of these data to human populations. [postscript] To help understand the difference itself and be able to extrapolate this information, neuroinformatics has been developed. This is an analysis that combines neuroscience, evolutionary science, statistical modeling and computer science (20). This analysis relates numeric values assigned to at least 10 mammalian species and the results can help to equate dates and integrate data in the neurodevelopmental literature across laboratory species to humans, and help to develop clinically relevant experimental models. This information is available on line (http://translatingtime.net). Second, consider experiments focusing on choline during pregnancy. In these studies the dose of choline used in the supplemented diet is a high dose (4× normal diet) but within the normal distribution; it is 4.6 mmol choline chloride/Kg/day (21), whereas the low choline diet, at least during pregnancy, still had enough choline to support the maternal needs. Thus, in the experimental model the distribution of choline intakes reflected the probable distribution range of choline intakes found in human populations. For example, in Californian women who consumed pre-conceptively less than 290 mg /day (lowest quartile) of choline in the diet had an increased risk of neural tube defects (NTD) at the end of their pregnancies, while controlling for other nutrients involved in DNA methylation (22). However, women in the highest quartile had intakes > 498 mg/day of choline and no cases of NTD reported. These choline intakes suggest that at least a 200 mg difference in the spread was sufficient to result clearly in deficiency and sufficiency/ supplementation outcomes. Of course, this spread could be even higher if the populations compared were from less well-nourished societies.

Question 5: Are these experimental models, which are based on comparing deficient vs. sufficient states, appropriate to assess the potential benefits of nutrients in populations with adequate nutrient intakes? **A.** Yes, to some extent these models can help us in understanding the tails in the distribution of nutrients intakes. The model is useful in providing a comparison between the extreme intakes, low vs. high, and thus determining a range of the intake. However, these models by themselves do not provide the information necessary to determine nutrient requirements in the population; other approaches are necessary (see following question and answer).

Question 6: Are current approaches to estimate nutritional requirements appropriate for assessing the nutritional needs of those individuals with low intakes or with specific needs? **A.** The current methods take into consideration a normal distribution of a nutrient intake in a “clinically healthy normal” population; this probability approach, assuming little variability between and within individuals and defining normal as the mean with ± 2SD, provides an estimate of the usual intake in 95% of the population. This approach, or using the Estimated Average Requirement (EAR) cut-point method approach, can provide estimates of prevalence of nutrient inadequacy when the distribution of requirements for the nutrient is symmetric around the EAR. However, these approaches cannot adequately identify subsets of the

population who differ in their requirements for a nutrient, for example individuals at the lower tail of the 95% distribution. To identify these common population subgroups that differ in nutrient requirements, it is probably necessary to use other approaches like nutrigenomic and metabolomic profiling (23). Nutrigenomic and metabolomic can help identify respondents from non-respondents and target them and avoid using recommendations for the entire population.

Question 7: Are current approaches appropriate for assessing the nutritional needs of brain specific outcomes like neurogenesis or synaptogenesis? **A.** These probability approaches tend to suggest intakes that must exceed the actual required intake for most of the population to ensure that those persons with the highest requirement ingest adequate amounts of the nutrient. In this regard, it is conceivable that the recommendation may cover all possible outcomes in a clinically healthy population. However, if a brain enhancement approach is utilized, the whole distribution of intake may be shifted and the recommended intakes would need to be evaluated. For example, in animal studies of choline supplementation in early life, the resulting improvement in brain performance and neurogenesis in the hippocampus was observed in the entire population; there were not subgroups of respondents or non-respondents, but the entire population was shifted (24). However, laboratory rodents are genetically homogeneous, while humans are not. Another approach is to study populations with unusual nutrient intakes in their natural environments. The argument here is that their diets have gone through a natural selection process to enhance survival. For example, Pauletto et al. (25) compared a population with a high intake of fish, and specifically fish oils, against a population consuming mainly a vegetarian diet and found a low incidence of cardiovascular disease in the population with highest intake of DHA in their diet. Similarly, the association between optimum DHA intake and brain function could be assessed in these populations. Although in these cases a single nutrient has been evaluated, it is important to consider nutrient-nutrient interaction as these micronutrients may share common pathways in cellular metabolism (4). Thus, it is important that these interactions and others be considered and studied when setting up studies of nutrient requirements for brain enhancement or brain function optimization.

Question 8: How do we develop a strategy to assess nutrient-brain enhancement effects in infants and young children? **A.** It will depend on the level at which there is evidence to support the proof of principle that a nutrient or neurotrophyc factor affects brain structure or function. A screening level will be a starting point. This can be accomplished by using *in vitro* culture models derived from rodents and human neuronal stem cell lines or immortalized human neuronal cells. These models can facilitate the screening of possible neurotrophic agents, nutraceuticals and nutrients having effects like neurogenesis and synaptogenesis. This can be enhanced by using a gene-expression profiling, which would indicate which genes are affected up/down. Next, it is important to determine if there are alterations in behavior; these alterations can lead to examine possible neuroantomical, neurophysiological or neurochemical abnormalities explaining the changes in behavior. Ideally, this could lead into identifying a gene that is associated with such a behavior. This requires *in vivo* animal models of behavior. Such models have been used to assess the developmental neurobehavioral toxicity of lead across species and in determining the validity of these models in providing inference to human behavior (26). Another alternative, if knowledge is available on the brain effects of individual nutrients, is to assess these nutrients in combination, and determine if their mix enhances brain effects. These *in vivo* experiments can also help to identify a period of flexibility or vulnerability in optimizing a brain function. This can be followed by observational studies in human populations with different dietary intakes of the nutrients in question and their association with neurophysiological and cognitive variables. A simple approach could include determining brain performance and cognition in toddlers and assessing their nutrient status, and then compared in a contingency table the difference among intakes (e.g., in quartiles) and

among their cognitive outcome (e.g., in quartiles) after controlling for differences in genetic and environmental factors.

Question 9: What is the best strategy to measure nutrient-brain effects in infants and young children? **A.** In order to determine that a nutrient(s) has an effect in infants and children, it is essential to demonstrate the role this nutrient(s) has on brain function and behavior in non-clinical studies. On this basis, the next step requires an integrated approach using a combination of specific methodologies that assess neuronal performance, neurobichemistry/ neurometabolism and behavior.

Question 10: What is best way to measure nutrient-related behaviors? **A.** This includes the assessment of the cognitive processes – perception, attention, language, memory, and the organization of action. There are new improved technologies for studying how these higher functions are organized in the brain and how they are related to the neurobiology and brain function. However, less progress has been made in measuring cognitive abilities during the toddler years. In part, this is because development in this age range is associated with greater independence of behavior and less willingness to cooperate. In assessing attention, it is important to include measures that assess its different components (i.e., alertness, visual orientation, object perception and endogenous attention) as each of them has different ontogenic development during post-natal life (10). Working memory, the capacity for holding information for immediate processing, emerges during the first year. This is another behavior-metric that can be assessed (e.g., delayed-response tasks in which the infant sits on the parent's lap in front of a screen containing two windows and demonstrates working memory by gazing at the location where an examiner disappeared (27). Thus, attention and working memory can be included as measures in studies of nutritional effects in behavior and cognitive development in 1-3 year old children. Additionally, laboratory procedures in which observational technologies like eye movement monitoring and physiological measures like ERP or MRI are incorporated together will provide sensitive analysis of nutrient brain effects on behavioral development. Finally, i technologies for assessing cognition must be transferred from the laboratory to translational contexts (e.g., to evaluate parent's satisfaction with child's school work).

Summary

The explosion in new knowledge about the genetics, structure, and function of the brain challenges nutritional scientists to better understand how nutrients affect or enhance brain development and behavior. Nutrition is considered a relatively young science compared to chemistry, biochemistry and physics. Approximately 100 years-ago food derived vitamins were discovered and scientists have spent a century exploring the mechanisms of nutrition. The goal has not changed: nutritional scientists must engage technological prowess in order to assess the efficacy of nutrients and food-derived neurotrophic ingredients in enhancing brain growth, development and performance. Today's challenges include expanding our knowledge on how nutrients affect brain structure, function and behavior (brain-effects), developing strategies to identify alternative nutrients with brain-related effects, and optimizing nutrient recommendations to include brain effects as an outcomes of growth and development in infants and pre-school children. Multidisciplinary perspectives, such as those presented in this symposium, are very helpful, and this is a first initiative in bring industry and academia together to identify the gaps in our understanding and suggest new approaches to filling these gaps and developing strategies and technologies to assess how nutrients affect behaviors during the entire life span.

The present symposium offers the important observation that the spectrum of nutrients with brain effects has not changed much in the last 25 years. That is, iron, iodine and zinc are still

the metals with proven brain effects. Among vitamins and fatty acids, the list is larger but not notably different from the past except for the recent data supporting the brain effects of DHA, choline and possibly vitamin B12. However, technological advances in neuroimaging and developmental psychology have helped advance our understanding of the role of brain regions in cognitive functions. Thus, these technologies help us to better understand the mechanistic pathways of these nutrients and to link these pathways to cognitive functions. A clear example of this is the use of ERP studies to show that infants of diabetic mothers have impairments in memory from birth through 8 months of age that are consistent with alterations in mechanistic pathways of memory observed in animal models of perinatal iron deficiency (28). Also, we identified the need for nutritional scientists to better understand the mechanisms by which nutrient enhancement can help optimize brain effects. In this regard, gaps in knowledge remain in our understanding of how nutrients and neurotrophic factors can interact with each other in optimizing brain development and function. In tandem, it is important to consider the safest manner in formulating these nutrients into food-products for infants and children in ways that contribute to their mental well being and reduce their risk of adult mental illnesses.

Innovations in infant and childhood nutrition can provide infants and children with the best possible start in life. The innovations resulting from the advance of knowledge in the scientific community are a challenge for the manufacturer. This challenge can vary from simple technological advances like the inclusion of a new ingredient to the conceptualization and rethinking of the entire product, and thus it may require considerable investment (29). The next step is capitalizing on the usefulness of innovation while maintaining the safety of the product in both pre-clinical and clinical studies using standardized protocols that explore relevant outcomes. The time needed for fulfilling these tasks and their costs may be viewed differently from the perspectives of academia and industry, and because of this diversity the close co-operation between academia and industry is necessary in order to convert emergent ideas into innovative products in a timely and cost-effective manner. Biomedical research takes place in universities, in government laboratories, and in the laboratories of companies, but only industry translates these innovations into products (30).

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Table 1

Topics and issues addressed in workshop No.1

Session	Presentation Topics	Directives
Theme: How do nutrients alter Brain Function? Mechanistic pathways and experimental models	• Trace Metals in the Developing Brain **a.** Effects on neurogenesis, apoptosis and plasticity • Origins of modern Homo Sapiens and Docosahexaenoic acid (DHA) **a.** Consumption of DHA-rich diets and appearance of civilization • Prenatal Choline Availability, Neural Plasticity, and Memory **a.** Early experiences and Sources of variability in Choline: Developmental Brain Plasticity • Glycemic Extremes and the Developing Brain **a.** Brain structural effects of glycemic extremes	• Making inference on other less studied nutrients based on current knowledge of nutrients with brain effects: Effects on neurogenesis, synaptogenesis and plasticity • Factors affecting the variability in nutrient requirements for brain effects: Implications of these sources of variation on studying nutrient brain-effects. • Defining critical or sensitive periods in toddlers and young children: Do these periods apply to specific nutrient or for all brain-effect nutrients, and which nutrients are the most important? • Experimental approaches for assessing the role of nutrients in brain development and function: Their application and inferences to studying the brain-effects of nutrients in sufficient and deficient populations **a.** Do these experimental approaches mimic toddler's mental milestones?

Table 2

Topics and issues addressed in workshop No. 2

Session	Presentation Topics	Directives
Theme: Methods available for studying the effects of nutrition on brain development and behavior in humans	• Measuring Memory and Cognition in Infants and Toddlers **a.** Working memory relevant-phenomena in infants and toddlers • Attention as an Outcome Measure in Studies of Nutrition **a.** Measuring functional components of attention in infants and toddlers • Event-Related Potential (ERP) as Tool for Studying Human Brain Development **a.** The goal of developmental neuroimaging • MRI Processing: Defining Neuromorphometric Endophenotypes for Genetic & Developmental Studies **a.** NIH MRI study of healthy brain development: Developing normative data in infants and children	• Inference (forward/backward) from these tools in assessing brain structure and function to behavioral changes • Reliability and accuracy of new tools for measuring brain functional outcomes related to nutrients having brain effects and subsequent effects on behavior. **a.** Implication of using these methods in understanding the relationship between brain regions and behavior. **b.** Are these methods sensitive enough to measure nutrient brain effects? • Factors affecting the applicability of these methods to infants, toddlers, and children • Technological problems in translating these methods from a laboratory environments to a school-work scenario • Identifying normative data on brain development and characterize behaviors in infants and young children to develop specific milestones