Caring for the Preterm Infant: Earliest Brain Development and Experience

Heidelise Als, Ph.D.

Department of Psychiatry, Harvard Medical School

Neurobehavioral Infant and Child Studies, Children's Hospital Boston

Presented at the

43rd Annual Meeting of the Japanese Perinatal and Neonatal Association

Tokyo, Japan, 8 – 10 July 2007

Sections of this paper have been adapted from the German publication Als, H. and Butler, S. Die Pflege des Neugeborenen: Die frühe Gehirnentwicklung und die Bedeutung von frühen Erfahrungen. In K.H Brisch and T. Hellbrügge (Hrsg.), *Der Säugling – Bindung, Neurobiologie und Gene.* Grundlagen für Prävention, Beratung und Therapie. Klett-Cotta, Stuttgart, 2008. pp 44-87.

Supported by Grant Sponsor: NIH/ NICHD; Grant Number: R01 HD047730 and R01 HD046855 (H.Als). Grant Sponsor: US Department of Education/OSEP; Grant Number: H324CO40045 (H.Als) Grant sponsor: I. B. Harris Foundation (H. Als). Grant Sponsor: NIH/MRDDRC Grant Number: P01HD18655 (M. Greenberg)

Correspondence: Heidelise Als, PhD, Enders Pediatric Research Laboratories, EN 107, Children's Hospital Boston, 320 Longwood Avenue, Boston, MA 02115

Telephone: 617-355-8249; Fax: 617- 730-0224; E-mail: heidelise.als@childrens.harvard.edu

Abstract

The prematurely born infant exchanges the womb environment for the Newborn Intensive Care Unit (NICU) at a time of very rapid brain development. Preterm neuro-development is pro-actively enhanced by avoidance of over-stimulation, stress, pain, isolation, and deprivation and by support to the individual infant's self-regulatory competence, strengths, initiative, and goal orientation. The steady availability of reliable, consistent, and familiar caregivers, who support the parents as the infant's foremost nurturers, is critical to the success of improved brain development. Four historical[1-5] and six randomized controlled trials[6-12] report the effectiveness of developmental care in the NIDCAP model (Newborn Individualized Developmental Care and Assessment Program). One equivocal review's opinion aside,[13] the four randomized trials, which focus on infants born at or below 29 weeks gestation, are consistent in their results of improved lung function, feeding behavior, and growth; reduced length of hospitalization, and improved neurodevelopmental function. One of the randomized trials, a three-center study,[11] documents comparable results for transported as well as inborn infants; it moreover identifies enhanced parent competence and lower parent stress scores. Magnetic Resonance Imaging (MRI)[12] in a study of medically low-risk infants born between 28 – 32 week gestational age, shows enhanced fiber tract development in frontal lobe and internal capsule. Results of several of the studies with high and low risk samples, show for the experimental groups when compared to the control groups, significantly better APIB scores at 2 weeks after expected due date,[14,15] significantly better Bayley[16,17] mental and psychomotor performance scores at 3, 5[4] and 9 months[1,6,12] corrected age (CA), as well as significantly improved behavioral regulation including attention, social and object play, cognitive and spatial planning, affect and communication skills, as tested in a play paradigm (Kangaroo-Box).[1,6] Outcome at three years (CA)[18] in a Swedish NIDCAP trial shows significantly better experimental group than control

group performance in auditory processing and speech,[19] fewer behaviorally worrisome symptoms,[18] as well as better communication skills.[20] Outcome to age 6 years[21] shows continued advantage in functioning without developmental disability, mental retardation or attention deficits. It is safe to conclude that individualized developmentally supportive care in the NIDCAP-model, based on substantive scientific evidence, improves early brain development, functional competence and quality of life for preterm born infants and their families, and is cost effective for the health care and later education system alike. Introduction of the NIDCAP approach into a hospital requires system change and is similar to a revolution. It requires a paradigm shift and considerable energy, commitment and resources at all levels of the organization. It may also require physical adaptations. Foremost, however, it requires education and guidance for the professional caregivers, physicians, nurses, and all other disciplines in the NICU alike. It leads to redefinition of the professional caregiver's role from that of efficient task orientation to relationship-based engagement with reflection in action. The NIDCAP model is highly compelling from a humane, ethical, family centered care perspective, and holds promise to become the new standard of all NICU care. In its center is the tiny, immature, dependent, and simultaneously rapidly developing human infant with a highly sensitive nervous system, who unconditionally trusts in the parents' and professional caregivers' full attunement and continued investment. Therein lays the great challenge and the great opportunity of all future developmental NICU care.

Introduction

Currently preterm birth, defined as birth before 37 weeks, is a global obstetrical challenge. About 13 million preterm deliveries occur per year around the world. The overall incidence is about nine percent.[22] In developed regions of the world the incidence varies from 5-12%. In Japan, the incidence is about 5-6%, i. e. relatively low, probably due to the excellent prenatal care available and the high reliability of Japanese women who take advantage of prenatal care. Incidence of prematurity may be as high as 40% in less developed, poor areas.[23-25] The incidence is steadily rising in the richer Western countries with the advent of extensive infertility treatment and women's increased age at child bearing. For reasons of generational poverty and stress associated with discrimination, as well as lack of ready access to health care, the incidence stands at an all time high of 18% for African-American families. Given the significant advancements in perinatology and neonatology in industrialized countries, survival rates have dramatically increased even for very low and extremely low birth weight infants. Today, more than 95% infants born before 28 weeks gestation, 12 weeks too early, and under 1250 grams, survive. Infants born at 24 weeks have a survival chance of about 50% in modern tertiary care centers. In Japan, a fetus of 22 and 23 weeks gestation has the legal and human right to be resuscitated and cared for. This is the lowest statewide-enforced gestational age in the world. Major disability rates for infants born at or below 25 weeks stand at about 25%; for infants born at 25 – 27 weeks the major disability rate stands at about 15%. For infants born at 23 weeks, the probability of 'intact' survival, i. e. discharge home free of major disabilities, is less than 10 %. It is less than 25% at 24 weeks and 35% at 25 weeks. Not until 26 weeks is the rate over 50%. While these infants comprise only a small percentage of births, they add disproportionately to the mortality, morbidity, and cost of medical care and of long-term disability services.[26-28] Preterm-born infants experience a range of adverse physical, behavioral, and mental health problems. Previously it was believed that in the absence of major complications (large intraventricular hemorrhages, significant chronic lung disease, severe intrauterine growth restriction; necrotizing enterocolitis) over time these children would 'catch up'. Recent research suggests however that as preterm-born infants mature they remain and often become increasingly disadvantaged on many measures of neuro-cognitive function and processing. They show difficulties in terms of academic achievement, and in respect to behavior regulation as well as in social and emotional adaptation.[26,29-34] Hack [32] found that at age 8 years, children born preterm with a mean gestational age of 26.4 weeks showed a high degree of cerebral palsy (14%), IQ below 85 (38%), poor motor skills (47%), and visual disability (10%).

It is becoming increasingly clear that it is not enough to assure the survival of preterm born infants. The quality of life is a key responsibility of the professionals working in newborn intensive care nurseries. Care for preterm-born infants that goes beyond the assurance of survival and takes seriously the assurance of optimal outcome in the long term, requires thorough knowledge and understanding of the immature infant's neurological and neurobehavioral development. Such knowledge and understanding provides the necessary basis from which to foster appropriate long-term neuro-integrated functioning and well-adapted development. Only with attention to these aspects may infants and families be guaranteed more encouraging long-term outcomes. Fetal infants were once thought to function at a brain stem level. However, advancements in newborn medicine and child development, have pointed out that even very immature infants are complex, responsive, and active in eliciting social and sensory stimulation. They are competent in their attempts to regulate their own thresholds of reaction and response. Increasingly, clinicians and researchers seek to identify ways to assess such early born newborns in terms of their strengths, vulnerabilities, and prognoses, in order to develop the most appropriate recommendations for their early support and care. This paper provides a framework for the understanding of the preterm infant's individual neurobehavioral development, the delivery of care from a neurodevelopmental perspective, and the effects of individualized developmentally supportive care on the outcome for children born preterm.

I. The Preterm Infant, a Displaced Fetus

Understanding of the preterm infant involves understanding of the conditions that assure survival of preterm born human infants, the evolved expectations of early human brain development, the effect of the altered environments on early brain development, and the essential social nature of human development.

A Neurodevelopmental Framework

Preterm infants are fetuses, who develop in extra-uterine settings at a time when their brains are growing more rapidly than at any other time throughout their life span. They expect three securely inherited environments, their mother's womb, their parents' body, and their family and community's social group.[35] Preterm delivery has removed these infants from their promised and expected environments. Given their organ immaturity, they require care that is available only in the specialized, medical technological environments of newborn intensive care units (NICU) and special care nurseries (SCN). Preterm infants in these unexpected intensive care hospital environments, experience that the very intensive care procedures that assure their survival, at the same time put them at high risk for significant organ damage. The most devastating include chronic lung disease or bronchopulmonary dysplasia (BPD), bleeding into the brain or intraventricular hemorrhage (IVH), scarring and/or detachment of the retina or retinopathy of prematurity (ROP), and gangrenous deterioration of the intestines or necrotizing enterocolitis (NEC). Aside from such damage, the mismatch of the fetal brain's expectation for the womb environment and the characteristics of the intensive care nursery provide significant challenges for the immature infant's development, and significantly influence the infant's neurostructural, neurophysiological, and neuropsychological development, with all the mental and emotional functions entailed in these domains.

Fetal infants expect to experience continual sensory and kinesthetic input from the amniotic fluid and the continuously reactive amniotic sac. These provide for appropriate intrauterine motor system development. Fetal infants also expect maternal diurnal and hormonal rhythms, which provide appropriate intrauterine differentiation of states of consciousness and guarantee the muted inputs and experiences that prepare the primary senses of hearing, smelling, taste, and seeing. In the preterm born infant, the taken for granted sensory experiences, are abruptly removed along with the sensory inputs, which were expected evolutionarily in a scaffolded time line. In addition, instead of the gradated stages of parental physiological, hormonal, and emotional preparation for the delivery of the fullterm infant, parental disruption is also sudden and often completely unexpected. This further adds to the challenge of in-NICU adaptation for preterm infants and parents. Even in medically low-risk preterm infants, these challenges lead to increased developmental difficulties later on. They include specific learning disabilities, lower intelligence quotients, executive function and attention deficit disorders, lower thresholds to fatigue, more visual motor impairments, spatial and computational processing disturbances, language comprehension and speech problems, emotional vulnerabilities, and difficulties with self-regulation and self-esteem. All of these add up to result in significant school performance deficits in more than fifty percent of preterm-born children.[26,29,30,32,34,36] It appears that development in the extra-uterine environment is highly challenging. It appears to lead to potentially quite maladaptive developmental trajectories. It is therefore important to discover whether and how one might assure smooth and balanced functioning for the fetus, who develops outside of the womb. Such strategies might prevent some of the mal-adaptations observed in preterm-born children. The evolutionary-ethological hypothesis states that improved understanding of the neurodevelopmental expectations of the fetal infant as expressed in the infant's behavior will provide the best and most reliable basis for developmentally appropriate modification and adaptation of traditionally delivered newborn intensive care and environments.

Early Brain Development and the Importance of Brain-Environment Interaction

The environment influences the development of the fetal brain through the infant's various senses, including the infant's visual, auditory, cutaneous, tactile, somasthetic, kinesthetic, olfactory, and gustatory senses. Increasingly animal and human studies point to the important role that sensory information and experience in the womb plays for the complexity of fetal brain development. The sensory environment outside the womb presents starkly contrasting and fully unexpected challenges to the fetal brain and thus appears to lead to malfunction and distortion of brain development and therewith of neurobehavioral functioning.

Human cortex begins development around the sixth week of gestation, when the embryo is less than 1.5 cm in length, with the arrival of primitive corticipetal fibers. The establishment of a superficial, primordial plexiform layer follows this. Cortical layer I, part of the plexiform layer, appears to be necessary for the subsequent inside-out formation of the cortical plate. Cortical layer I represents the actual mammalian neocortical gray, and appears to play a significant role in the overall structural organization of the mammalian cerebral cortex. It controls the migration of all future neurons regardless of size, cortical location, or functional role.[37]. By six weeks the superficial musculature of the embryo is highly developed,[38] as Figure 1 shows.

Figure 1

The cutaneous innervations and the development of the skin's sensitivity are well on their way.[39] They begin with sensitivity in and about the mouth, and from there extend to nose and chin, eyelids, palms of the hands, the genitalia, and the soles of the feet. They set up feedback loops and dynamically build the highly complex human central nervous system. Throughout development, a disproportionately large area of somato-sensory cortex is dedicated to the earliest innervated surface regions, and supports their specific evolutionary significance. It is these regions that appear difficult to satisfy and inhibit behaviorally in the fetal infant outside the womb.[40] Preterm infants brace with their feet, grasp with hands and feet, bring their hands to their mouths, search with mouth and tongue, suck, and make strong efforts to tuck themselves into flexion. This is especially apparent in the first 24–48 hours after delivery, before exhaustion leads to flaccidity and often-misunderstood lethargy.

Gesell[38] sixty years ago documented the organized specificity of very early fetal behavior, as shown in Figure 2.

Figure 2

He showed specific turning away to hair probe touch, while exploratory approach movements appeared to dominate spontaneous undisturbed activity. This early appearance of the avoidance and approach continuum is in keeping with Denny-Brown's[41] model of motor system development. It involves the gradual differentiation and subsequent re-integration of the dual antagonist extensor and flexor, i.e., avoidance and approach, movements. Ultrasound studies increasingly document the differentiating spontaneous movement repertoire of the fetus. They document the extensive and frequent flexor-extensor adjustments. They show complex grasping and release sequences; interaction with the continuously available, pliable, and moving umbilical cord; exploration of face, neck, and head; sucking, holding on with one hand to the other, stepping, and clasping one foot against the other; and many other such complex movement patterns. Such patterns set up increasingly complex feedback loops, and in turn generate the species-specifically complex human neuro-cyto-architecture, with its enormously enlarged frontal-cortical brain systems.

Each of the millions of neurons in human cerebral cortex originates in the germinal lining of the ventricular system. In its prime, the germinal matrix releases as many as 100,000 cortical neurons per day, each of which migrates through the entire thickness of cortex to specific locations. These migrations occur in waves. They begin at around eight postovulatory weeks and gradually tail off around 24 weeks of pregnancy, when neuronal maturation and organization increases dramatically. Much of neuronal maturation and organization for the preterm infant occurs in the interaction with the extrauterine rather than intrauterine environment. Each of the estimated 100 billion (or quintillion) total human neurons, once migrated to their respective locations, develops dendritic and axonal interconnections with an average of 100 other cells. The first synaptic contacts are established as early as 7 weeks. New cortical cells are generated at a low rate beyond 40 weeks and throughout the lifespan in hippocampus and possibly other specific brain areas. Synapses are established richly until age 5 years, more slowly, at least until age 18 years, and as now known throughout the life span.[42] As cells become larger and more elaborately connected, more and more sulci and gyri develop. Different brain areas organize differentially for increasingly more specialized functions. A marked increase in the number of gyri occurs at the end of the second trimester. This correlates with a concurrent growth spurt of the brain in terms of weight and a change in head contour from oval to prominent bi-parietal bossing. This is also the time, when fetal behavior becomes increasingly complex with increased sucking on fingers or hand, grasping, extension, and flexion rotations, increasingly discernible sleep and wake periods, and reactions to sound.

Special cells, the oligodendrocytes, grow and deposit myelin, a fatty sheath somewhat like insulation, around the axons. Myelination allows for fast conduction especially of highly repetitive impulses. It serves to accommodate the increased length of the neuronal tracks with growth. It increasingly speeds up processing time. Myelination occurs with peak activity around fullterm birth, and continues significantly until age 9 years and perceptibly into the 40s.

Concurrent with the processes of cell differentiation and myelination, neurobehavioral differentiation and neurochemical development occurs. Passage of impulses or messages between cells occurs by chemical neurotransmitters, which often are released only if up to four or five different regulatory systems concur in specific configurations. More than two dozen neurotransmitters have so far been identified and no doubt there are many more. The sensitivities and densities of neurotransmitter receptors vary widely from brain region to region. Experience influences receptor development. Structural and functional development of brain and sensory organs are interactive and interdependent. The vulnerability of the support structure tissue (glia and subplate neurons, see below) adds to the picture of sensitivity and fragility of the preterm brain and the consequent sensitivity in overall functioning. Up to 50% of preterm infants born before 32 weeks have some degree of brain hemorrhage and the incidence increases with the reduction in gestational age.[42]

Animal models have provided substantial evidence for the fine-tuned specificity of environmental inputs necessary for support of normal cortical ontogenesis in the course of sensitive periods of brain development and in the absence of focal lesions. Furthermore, differential cell death and other regressive events, which begin around 24 weeks gestation with the tailing-off of cell migration, appear to be of key importance in sculpting developing cortex. The developmental timeline of these normally occurring regressive events causes them to be affected directly by premature birth. Of interest in this regard is also the function of sub-plate neurons. Subplate neurons are born in the generative zone and migrate to the primitive marginal zone before generation and migration of the neurons of the cortical plate themselves.[42] Sub-plate neurons provide a site for synaptic contact for axons ascending from the thalamus and other cortical sites, termed “waiting” thalamo-cortical and cortico-cortical afferents, because their neuronal targets in the cortical plate have not yet arrived or differentiated. Sub-plate neurons are strongly involved in cerebral cortical organization. The sub-plate neuron layer in frontal human cortex reaches its peak at 32 to 34 weeks of gestation, a time the preterm infant spends outside of the womb where the infant experiences quite unexpected sensory inputs, which reach primary cortical areas. For instance, visual cortex in the womb would have received no light or patterned input until 40 weeks, while the preterm born infant receives unexpectedly very bright light in the delivery room and then in the NICU. Preterm infants' still fused or close eyelids are very thin and highly light permeable, thus do not protect visual cortex from light stimulation. Somato-sensory or auditory cortices on the other hand do receive inputs in the womb, yet these inputs are modified considerably from those received from the same stimulation source outside the womb.

In the fullterm child, axonal and dendritic proliferation and the massive increase in outer layer cortical cell growth and differentiation leads to the enormous gyri and sulci formation of the human brain. This occurs in an environment of mother-mediated protection from environmental perturbations. It relies on a steady supply of nutrients, temperature control, and the presence of multiple regulating systems, including hormonal and maternal-fetal chronobiological rhythms. The traditional NICU environment, despite its great advances, continues to be a grossly inadequate substitute for the well-functioning human womb. On the one hand, the NICU involves massive sensory overload along certain dimensions, such as sound and light, on the other hand it is lacking entire dimensions of regulatory inputs that the fetal brain relies on, such as the fluid environment, maternal hormonal input and many others. Thus, the NICU stands in stark mismatch to the developing nervous system's expectations.[43] Resultant prolonged diffuse sleep states, unattended crying, supine positioning, routine and excessive handling, ambient sound, lack of opportunity for sucking, poorly timed social and caregiving interactions and many others, all exert deleterious effects upon the immature brain and alter its subsequent development. The questions becomes: How may one understand the mechanisms and processes of the extrauterine effects, estimate the potential effects on the individual immature infant's nervous system, and how does one therefore diminish the deleterious impact?

It seems warranted to hypothesize that messages transmitted from primary cortical regions to other cortical areas, including prefrontal cortex, are quite different for the preterm infant in the NICU than they would be for the fetus in the womb. It is likely that waiting (subplate neuron activity) and regressive events (cell death) are modified when the brain finds itself in unusual sensory circumstances, such as too early outside of the womb, and that cells are preserved, which otherwise would be eliminated, and cells are eliminated, which would otherwise be preserved. Monkeys delivered experimentally prematurely, while unchanged in visual cortical cell number, show significantly different cortical synapse formations, in terms of size, type, and laminar distribution, when compared to fullterm monkeys tested at comparable post term ages. The extent of difference correlates with the degree of prematurity.[44] Thus, while some events influence neuronal migration per se, other events, including differences in sensory input, appear to alter cortico-cortical connectivities and lead to unique cyto- and chemo-architectures of cerebral cortex. This supports the finding that preterm infants show brain-based differences in neurofunctional performance due to difference in experience. Premature activation of cortical pathways appears to inhibit later differentiations and to interfere with appropriate development and sculpting, especially of cross modal and prefrontal connection systems implicated in complex mental processing, as well as attention processes and self-regulation. Furthermore, corpus callosum differences have also been documented in preterm children studied at school age.[28]

The Social Environment of the Human Newborn

Parents are keen and sensitive in aiding their newborn infant in stabilizing alertness. Mothers will typically acknowledge with delight even brief eye opening. At such acknowledgment infants may avert their gaze, yawn and sneeze, or fuss and cry, and thus reset the interactive intensity to a lower level. Infants, who stay locked on the mother's face, may gradually tense, spit up, hiccough, gag, or move their bowel, reacting at a generalized autonomic visceral level. Or else they may extend and flail, squirm, and arch, and utilize motor system shifts in tone and activity and thus reset the intensity of the interaction. Some infants sustain alertness for substantial periods supported by well-regulated behavioral subsystems. In such cases, the mother may be the one to reset the intensity of attention and interaction. She may draw the infant close, nuzzle and kiss, stroke or pat the infant,[45,46] as Figure 3 depicts.

Figure 3

From the very beginning of extrauterine life, the newborn is launched onto the species specific, interactive, collaborative, and communicative track, which is supported and affectively rewarded by the caregiver. Newborn interactive attention appears to be of high species value.[47]

Differences between Preterm and Fullterm Born Infants

Differences between preterm-born and fullterm infants are manifest in all dimensions of neurodevelopment, namely neurobehavior, neurophysiology and neuro-structure.

Neurobehavioral Differences: Infants born early often show great reluctance to come into alertness. They may demonstrate hypertonic, flexed, high guard arm positions with fisted hands, become pale, breath rapidly and unsteadily, and show pained, drawn facial expressions.[48] With slow, calm support they may gradually open their eyes. At the same time the hypertonic, high-guard fisted, defensive posture may shift abruptly into flaccidity and tuning out. The infant may pale further, and breathe slowly and unsteadily. The attention mustered will likely be glassy-eyed, strained, and barely focused. The cost to the autonomic and motor system regulation will be high. This pattern of relatively poor subsystem differentiation, in which all systems react in a generalized fashion, exemplifies the overall cost for even a small accomplishment, such as eye opening. Measurement of subsystem involvement in specific performances is important in understanding an infant's current competence on the infant's developmental trajectory.

The Assessment of Preterm Infants' Behavior (APIB)[14,15] is a comprehensive newborn behavioral assessment. A number of studies have demonstrated the APIB's sensitivity in differentiating subgroups of infants of varying gestational ages and degree of risk status. All infants were assessed at 2 weeks corrected age.[1,6,7,9,49-52] The APIB has also detected highly significant, cross-sectionally assessed, developmental differences between medically low risk infants born at varying gestational ages (34, 37 and 40 weeks).[52] The APIB thus provides significant information for clinical care and support. Furthermore, Als and her collaborators.[53] studied a large number (n=160) of preterm and fullterm infants at 42 weeks postmenstrual age, fullterm infants, preterm infants between 32 and 37 weeks, and extremely preterm infants (< 32 weeks). The three gestational-age-at-birth groups of infants were significantly different across all APIB system scores. The fullterm infants scored best in all six behavioral systems; i.e. they were the most well-modulated and well-differentiated infants. The earliest born infants scored worst in all six behavioral systems, i. e. they were the most sensitive and most easily disorganized group of infants. The middle gestational age at birth group of infants on all systems took a middle position.

Electrophysiological Differences: The APIB furthermore showed strong concurrent validity when paired with EEG cortical coherence measures. Duffy[51] demonstrated strong concurrent validity between APIB and EEG coherence measures in sleep as well as in awake states. The sample consisted of 148 healthy preterm and fullterm newborns, who were studied at 42 weeks postmenstrual age.[51] The behavioral and electrophysiological differences, all in the direction of amplitude reduction, point to the decreased adequacy of functioning for the preterm infants in comparison to the full-term infants. EEG topographic mapping, independently performed from unrestricted cortical coherence measurement[12,54] documented the same findings.

Brain Structural Differences: The APIB also showed strong concurrent validity with brain structural measures derived from magnetic resonance imaging (MRI). Preterm and fullterm infants differ in cortical gray and white matter as well as onset of myelination in the last trimester.[55] Hüppi et al. reported the use of the APIB in association with magnetic resonance imaging (MRI) in comparing at term low risk preterm and healthy term infants.[56] She reported preterm reduction in myelination and gray-white matter differentiation as well as poorer performance on six out of six APIB system scores in the preterm infants when compared to the fullterms. In addition, fetal growth restricted (FGR) preterm infants at term when compared to appropriately grown (AGA) preterm infants at term[57] displayed poorer MRI based neuro-structural and poorer APIB neuro-functional measures.

Quantitative MRI studies, which investigated preterm infants with white matter injury, found that those preterm infants born very early and those with fetal growth restriction, showed significantly decreased gray matter volumes.[58-60] Furthermore, these changes were found to be associated with impaired neuro-developmental outcome.[58] Preterm infants, with somewhat longer gestations to the time when neuronal migration to form cortex is largely completed (28 – 33 weeks), decrease in gray matter volume found may be caused by atrophy and neuronal loss, and/or by disruption of the formation of neural connectivity and/or by disruption of dendrite growth during synaptogenesis.[61-63]

In comparison of preterm and fullterm infants' brain tissue volumes, Mewes and her associates[64] reported, based on MRI assessment, biparietally narrowed and fronto-occipitally elongated head shapes in infants' born preterm (28 to 33 weeks gestation). A regionally increased CSF volume accompanied this difference in head shape. Bi-parietal flattening occurs in response to external compression force such as is exerted during supine sleep position in incubators and cribs[65] for infants born preterm, who have weaker neck and head control than full-term born infants.[66-68]

Mewes and her associates[69] also found evidence that low-risk AGA preterm infants (28 to 33 weeks gestation at birth) showed moderate regional volume distribution differences for white matter development in comparison to healthy fullterm infants. In contrast, the regional volume distribution of gray matter development was not affected in the population studied. The investigators reported a daily increase in overall cerebral tissue volume of 3.2 ml from 32 to 42 weeks LMP. Longitudinal analysis of preterm infants' serial data demonstrated that the brain tissue composition changed from 32 to 40 weeks PMA and presented a decrease in regional distribution of unmyelinated white matter in favor of gray matter growth. Longitudinal analysis of the brain tissue composition suggested that the period under study might be critical for gray matter growth. Since neural migration itself gradually ends by the beginning of the third trimester, the pronounced increase in gray matter volume may indicate the increasingly rich axonal branching and developing connectivity between neurons as well as synaptogenesis.[70-72] Furthermore, overall volume growth was most rapid in the frontal and occipital regions. The investigators also found that the low-risk preterm infants, who have head circumferences appropriate for their post-menstrual age, when studied at 2 weeks corrected age, had cerebral volumes comparable to those of healthy fullterm newborns studied at the same age, yet had significantly increased CSF volumes. The same study also found that a decrease in the fraction of unmyelinated white matter of total white matter did not systematically correspond to an increase in the myelinated fraction of total white matter. Whether unidentified injury, delay, or an alteration of fiber tract development causes these differences is not known at this time.

The newborn period findings of brain differences in preterm born infants compared to fullterm infants continue into infancy and school age. Brain imaging studies of a sample of AGA and FGR preterm infants at early school age and into adolescence have shown generalized thinning of corpus callosum (CC) in association with word production difficulties[73-75] and clumsiness.[76] A recent MRI study that compared preterm with fullterm born children[77] at age 8 years also showed

CC differences. Significant volume reduction was also identified in basal ganglia, amygdala, and hippocampus, even in the absence of intraventricular hemorrhage. These volume reductions correlated significantly with reduction in Full-Scale IQ. Sensorimotor cortex and mid-temporal brain volumes were most strongly associated with Full-Scale, Verbal and Performance IQ. Gestational age significantly correlated with deficits in right and left sensorimotor cortices and right amygdala. A volumetric comparison study of the cerebellum of very preterm and fullterm adolescents identified significant overall volume reduction for the preterm-born children.[78] Cognitive test scores showed strong association with cerebellar volume reduction. This suggests that preterm cerebellar dysfunction may be associated with disrupted cognitive function, and likely be due to the many reciprocal connections between the cerebellum and other brain areas.

II. Changing the Future for Infants Born Preterm

Given the significant differences identified between preterm and fullterm infants when studied at comparable ages, it becomes obvious that the next big challenge is the reduction of the discrepancy of the extrauterine NICU experience and the preterm infant's brain's expectation. The questions become: How do we know what the infant expects and whether we understand the infant correctly? How do we modify the environment and the experience of care in the NICU? In addition, if we do so, does it make a measurable difference?

Observing Preterm Infants' Behavior: Synactive Theory of Development

The infant's behavior is the always-observable access route and communication vehicle to understand the infant's brain function, as Figure 4 depicts.

Figure 4

It is the means by which the infant expresses how the infant feels, whether the infant is currently thriving or suffering. According to Denny-Brown,[41] underlying the developing nervous system's striving for smoothness of integration is the tension between two basic antagonists of behavior, namely the exploratory and the avoiding response system. The two dimensions are released simultaneously and in conflict with one another. If a threshold of organization-appropriate stimulation is surpassed, one dimension may abruptly switch into the other. The two dimensions or poles of behavior are basic to all functioning. The existence of single cells in somatosensory cortex demonstrates this. Upon stimulation, these cells produce total body-toward or total body-avoidance movements. The same principle operates in the gradual specialization of central arousal processes, which in altricial animals lead to functionally adaptive action patterns such as suckling, nipple-grasping, huddling, and others.

This principle of dual antagonist integration is helpful when one wishes to assess preterm infants' behavioral thresholds from integration to stress. In the well-integrated performance, the two antagonists of toward and away modulate one another and bring about an adaptive response. When an input is compelling to the fetal infant and matches interest and internal readiness, the infant will approach the input, react to and interact with it, seek it out, and become sensitized to and receptive for it. When the input overloads the infant's neuronal network circuitry, the infant will defend against it, actively avoid the input, and withdraw from it. Both response patterns mutually modulate one another. For instance, the animated face of the interacting caregiver will draw in the fullterm newborn. As infants' attention intensifies, the infants' eyes may widen, their eyebrows rise, and their mouths shape toward the interactor. The infants' fingers may open and close softly. If the dampening processes of this intensity are poorly developed, as is the case in preterm infants, the whole head may move forward, and arms, legs, fingers and toes may extend toward the interactor, the mouth may shape forward, and the wide-eyed gaze may trigger the visceral system, so that the infant may hiccough or even vomit. The response, which fullterm infants largely confine to their faces and hands, in preterm infants may involve their entire body in an undifferentiated manner.

The overriding issue with which prematurely born newborns grapple is the integration of autonomic function, which includes respiration, heart rate, temperature control, digestion, and elimination, with the functioning of the motor system. Motorically infants seek to explore, feel contained, tuck into flexion, expand and extend, rotate, somersault, bring their hands to the mouth and suck, grasp the umbilical cord, etc. Preterm infants' motor systems expect cutaneous input from the amniotic fluid and amniotic sac wall, which *in utero* support the development and differentiation of increasing flexor-extensor balance. Preterm infants' state organization, furthermore, no longer is supported by maternal sleep-wake, and rest-activity cycles, or by maternal hormonal and nutritional cycles.

The model for the observation and assessment of behavioral subsystem differentiation, termed synactive,[40] highlights the simultaneity of the behavioral subsystems in negotiation with one another and with the current environment. Behavioral subsystems continually open up and transform to new levels of more differentiated integration. From there next steps of differentiation press to actualization.[40] Figure 5 shows the conceptual model underlying the synactive theory of development. To paraphrase E. Erikson (1962), self-actualization is participation with the world and interaction with another with a "minimum of defensive maneuvers and a maximum of activation, a minimum of idiosyncratic distortion and a maximum of joint validation."

Figure 5

Formulation of the Synactive Theory of Behavioral Organization.[40,79] takes into account the dynamic nature of all development as a process of continuous differentiation, integration, and modulation of the interrelationships of behaviorally observable subsystems of function. These in turn are always in interaction and interrelationship with the current environments. The synactive theory is at the core of the APIB (Assessment of Preterm Infants' Behavior), also developed in 1982 by H. Als, and as pointed out earlier, a neurobehavioral assessment of the individual infant's organization and competence. Competence is defined by the constructs of differentiation and modulation of subsystems of functioning and their respective integration.[15,80] The synactive theory views infants' functioning in a model of continuous intra-organism subsystem interaction, which in turn occurs in continuous interaction with the respective environment and thus is termed 'synactive'. At each stage of development, various subsystems of functioning exist simultaneously, while they mutually influence one another. Often their functioning is truly interactive. At other times, interactively supportive holding patterns provide a steady multi-system base for one of the system's current further differentiation. The systems addressed, as mentioned, include the autonomic, motor, state organization, and attention and interaction subsystems, as well as the self-regulation and balance subsystem. A further 'system' addressed is the environmental and caregiver/examiner facilitation required to bring about an infant's successful subsystem reorganization. Functioning of sub-systems is reliably observable without technical instrumentation.

Behavioral Language of the Preterm Infant

Observation of preterm infants' behavior provides a way to infer the infant's developmental goals and to assess the infant's current functional competence. Even very early born and fragile infants display reliably observable behaviors along the lines of the three main systems, the autonomic system, the motor system, and the state system with special emphasis on the emerging attention system. The autonomic system's behavioral communication signals include breathing patterns, color fluctuations, and visceral responses such as spitting up, gagging, hiccoughing, bowel movement strains, and actual defection, among others. Figure 6 shows the differences in color.

Figure 6

The motor system's behavioral communication signals include muscle tone of trunk, extremities, and face with good modulation, flaccidity or hypertonicity; as well as postures and movement patterns, such as finger splays, arching, grimacing, or tucking together, grasping, among others, as Figure 7 indicates.

Figure 7

Furthermore, the behavioral communication signals of the infant's state system, which defines the infant's level of awareness, include the infant's range of states such as sleeping, wakefulness, and aroused upset; the patterns of transition from state to state, and the robustness and modulation of each of the states. Alertness and attention is the further differentiation of the awake state, as Figure 8 indicates.

Figure 8

The fourth system is the self-regulation system. Specific behaviors are depicted in Figure 9.

Figure 9

All these reliably observable behavioral communications provide valuable information for the clinician and caregiver in how to structure and adapt care and interaction, in order to enhance the infant's own competencies, strengths and signals of self regulation, well-being, and reaching out/initiation, and to prevent or diminish the infant's signals of stress, discomfort, and/or pain.[40]

Developmental NICU Care - The Newborn Individualized Developmental Care and Assessment Program (NIDCAP)

The Newborn Individualized Developmental Care and Assessment Program (NIDCAP) is an individualized developmental approach to environmental support and care, based on reading each preterm infant's behavioral cues, which leads to formulation of a plan of care with the goal to enhance and build upon the infant's strengths, and support the infant in areas of sensitivity and vulnerability. See the NIDCAP Federation's website www.nidcp.org for additional information. [81] The goal of the NIDCAP framework to early care is the improvement of long-term child and family outcome. The framework applies during the delivery process in the delivery room, admission to the NICU, and throughout the infant's hospital stay as well as the infant's transition home and the first few months at home. The comprehensive NIDCAP approach represents an approach and testable model for the decrease of the discrepancy between the immature human brain's womb expectation and the actual experience in a typical NICU environment.

The NIDCAP model aims to create a relationship-based developmentally supportive care environment for preterm infants and their families. The theory proposes that care-implementation, which takes into account the infants' strengths and thresholds to disorganization is supportive of long-term outcome. The model is based on three assumptions: (1) Detailed observations of infant behavior during daily care giving interactions and at rest, provide an important foundation for recommendations in how best to minimize stress, and optimize an infant's strengths and development. (2) Care-giving staff benefits from supportive education in implementing such developmentally based and observationally grounded recommendations. (3) Care giving staff benefits from supportive education in close observation of the infant's behavior and in collaborating with the infant and the infant's family. (4) Resultant adaptations of care may lead to better outcomes in infant medical well being, neurobehavioral functioning, parent functioning, and staff skill, satisfaction, and self-definition.

The NIDCAP Methodology

The NIDCAP methodology documents infants' continuous communications through the recording of detailed observation of infants' naturalistically occurring behaviors in the NICU.[81]

The naturalistic observation sheet (NIDCAP Sheet) provides a systematic format for the recording of the detailed observation of the individual infant's behavior every two minutes. Figure 10 shows a blank NIDCAP observation sheet.

Figure 10

Ninety-one behaviors represent the communication signals of the autonomic, motor, state, attention, and self-regulation subsystems. Typically, the infant is observed for about 20 minutes before a caregiver interacts with the infant, then throughout the duration of the care giving interaction, such as the assessment of the infant's vital signs, suctioning, diaper change, feeding, etc. Subsequently, the infant is observed for at least 20 minutes after the care giving interaction as the infant returns to a restful state. These observations, especially if repeated over time, yield much information regarding the infant's robustness and development, as the infant attempts to integrate and make the best use of the care provided. The observations lead to narrative written reports, which describe the infant's strengths, current sensitivities and thresholds to stress, and the infant's efforts to regulate him or herself. The observations provide the basis for interpretation of the infant's current apparent goals, and for suggestions regarding care giving and environmental adaptations, which may enhance the infant's goal achievements, increase the infant's strengths, and reduce the infant's stress behaviors.

The behaviors observed are conceptualized as behaviors, which evidence stress and those, which evidence competence. The behavioral descriptions of the infant's functioning are understood in the context of the infant's current medical status and history, as well as the family's history. The estimation of the infant's current developmental goals takes the history of infant and family into consideration. For instance, an infant, recently intubated and supported by a respirator, may actively seek to pull him or herself into flexion. The infant may seek to grasp, to tuck legs and feet into the bedding and against the wall or surface of the incubator, in an apparent attempt to find boundaries and security. The infant may seek to bring hands and fingers to and into the mouth in an effort to suck. An infant also may make efforts to breathe smoothly *with* rather than against the respirator, only to be challenged repeatedly by the fixed respirator rate setting. The infant may attempt to settle back into sleep and restfulness after being cared for, only to arouse repeatedly to sounds from alarms, faucets, voices, equipment being moved about, etc. Based on an infant's observation, the observer, in collaboration with the infant's professional care providers and the infant's family, then formulates a statement of the infant's goals. Based on the goals inferred from the infant's behaviors observed, opportunities to better support the infant are then explored. These include consideration of the infant's room environment, in terms of lighting, sound sources, temperature, traffic, etc; the infant's immediate bedside environment, in terms of comfortable chairs or beds for the parents, siblings and other family members, layout of shelving, storage bureaus, décor, etc. ; comfort of bedding, adjustment and comfort of tubes, lines, IV boards, etc.; and the infant's social environment in terms of timing, gentleness, supportiveness, and slowness of all human interaction and all interactive care delivery. The suggestions made will be always aimed to support the infant's well being, strengths, sense of competence and effectiveness, and therefore support the infant's optimal development. The considerations begin with appropriate support and nurturance for the infant's parents and family. They are the primary co-regulators and nurturers of the infant's development. Next, the atmosphere and ambiance of nursery space, of care, nurturance, and respect for infant and family in the NICU environment are considered. The organization and layout of the infant's care space is the next topic of consideration. Then follow the topics of structuring and delivery of specific medical and nursing care procedures and of any specialty care procedures as may be indicated. Throughout, the overall safeguarding and assurance of a developmental perspective on care and environment is the foremost consideration. A more detailed description of this approach is available elsewhere.[80,82-84]

The assurance of the parents as the primary nurturers of their child is crucial to the infant's developmental outcome. The support and sensitization of the parents to their child's behavior and its meaning is essential to the appropriate implementation of the NIDCAP model of care. For example, the infant's hospital space often is the infant and parent's home for three to four months. Organization and layout present critical opportunities for support and nurturance of infant and family. Parents and infants seek respectful, supportive, professional and consistently nurturing environments in the NICU that help them grow in their role as competent parents and infants, and become well-functioning mutually supportive and trusting families. Increasingly, nurseries are beginning to build individual private family care rooms for each infant and family. Figure 11 shows an infant cared for by her mother in skin to skin contact.

Figure 11

These 'womb rooms' provide opportunity for individually controlled temperature, lighting sound, privacy and comfort for infant and family, and for the specialty caregivers involved in the infant's and family's care. The implementation of this concept requires well educated and informed, as well as emotionally well-differentiated leadership and communication systems in order to assure privacy yet appropriate accompaniment, collaboration, and support for the family in nurturing and caring for their infant and themselves. Private bathrooms within the individual care room suites for the parents for instance are very important as well as meal facilities and rest and relaxation areas. Sufficient and ongoing detailed attention to the infant's neurodevelopment and the parents' psychological strengths, recovery and health is critical.

The transitions and transformations that developmentally supportive care demands in the NICU setting, involves the movement from a protocol-based framework to a relationship-based framework of care. The key concept of the relationship-based, individualized, developmental care framework is the concept of co-regulation, based in an evolutionary, theoretical framework and a neurobiological basis of the social, neuro-essentially interconnected nature of humans. Figure 12 depicts conceptually the shift to relationship based care as promoted in the NIDCAP model.

Figure 12

Implementation of a theory-guided rather than procedurally driven approach is challenging in any setting. It is especially challenging in an acute and intensive care setting such as the NICU. This is an environment, which is oriented, by tradition and original medical necessity, towards standards, protocols, strictly enforced rules, compliance, and care giving routines. A co-regulatory framework of care requires that caregivers are mindful of one another, mindful of the personhood of the infant and the family, and therefore reflective about their own actions and ways of being, while they nevertheless function effectively in an intensive medical care setting. The challenges of such a transformation and active practice in this model of care involve considerable staff education and professional technical and emotional support. The infant's care involves many procedures, examinations, and therapeutic, intensive interventions delivered by care giving staff from various disciplines. The infant's care involves not only safe and effective structure and implementation of care procedures, but the continuous embedding of all procedures in a developmental perspective, which extends to and encompasses all care and environmental aspects.

The staff's transition to the level of awareness of and attunement to the infant's and family's individuality and goals requires continuous staff support and education. Families, the environment, and the infants must be seen with new eyes. Staff must let go of earlier, well-practiced conceptualizations and routines, and become effective in and open to learning and practicing a new approach of engagement in a process of self-reflection, action in reflection, and reflection in action. Reflection as a framework of practice at first may appear foreign and almost subversive to those used to action-driven, fast-paced, adrenalin-dependent, intensive, technologically focused, medical care work. The implementation of NIDCAP developmental care transforms such care with time, support, and guidance, into reflective, self-aware practice with superb relationship engagement skill coupled with superb technical skill. NICU work involves intensive human interaction at many levels and in the complex interface of high intensive care, physical immaturity, and emotional vulnerability. Introduction of NIDCAP into a nursery involves system-wide investment not only in education and physical changes but also in transformation of all practice and relationships.

Empirical Evidence for the Effectiveness of NIDCAP

Four historical, and more recently six randomized controlled trials[6-9,11,12] have investigated the NIDCAP model's effectiveness. One ambivalent review[13] aside, the results provide consistent evidence of improved lung function, feeding behavior and growth, reduced length of hospitalization, improved neurobehavioral and neurophysiological functioning, and more recently,[12] enhanced brain fiber tract development in frontal lobe and internal capsule. Cortical coherence factor maps have demonstrated for the experimental (NIDCAP) group infants increased coherence between long distance, left frontal regions and occipital and parietal regions, whereas short distance, midline central to occipital coherence was reduced. The experimental group showed changes in functional connectivity between brain regions, with preferentially broad enhancement of frontal to occipital coherence (long distance coherences - newly emerging competences) and pruning of central to occipital coherence (short distance coherence - already well-integrated competence), as Figure 13 shows.

Figure 13

MRI study simultaneously showed much-enhanced white matter fiber tracts in internal capsule and in frontal lobe for the experimental group infants at 2 weeks' corrected age when compared to the control group infants, as depicted in an example in Figure 14.

Figure 14

A three-center trial[11] involved two transport and one inborn NICU. In addition to the earlier reported improved health and neurobehavioral outcomes that the other studies of infants less than 29 weeks gestation showed, this study also documented positive parent outcome results. They included lower parental stress, enhanced parental competence, and higher infant individualization by the parent. Several studies have demonstrated significantly better Bayley mental and psychomotor developmental scores at 3, 5[4] and 9 months[1,6] corrected age, along with improved attention, interaction, cognitive planning, affect regulation, fine and gross motor modulation, as well as improved communication. At three years corrected age a Swedish study[18] documented better auditory processing and speech (Griffith Developmental Scales), as well as fewer behavior symptoms and better mother child communication, and at 6 years corrected age[21] higher survival rates without developmental disabilities, specifically without mental retardation and attention deficits. Thus, the NIDCAP model appears to be based on sound, multi-pronged, and multi-study scientific evidence.

Randomized controlled NIDCAP trials require large NICUs in order to make feasible the study of control (standard NICU care) and experimental (intervention/developmental care) groups, and make feasible an experimental effect that exceeds the inevitable spillover or contamination effect that accompanies caregiver-implemented treatments. NIDCAP trials furthermore require expertise in the conduct of behavioral research, which is quite different from the expertise required to carry out typical biomedical trials. NIDCAP research requires not only experienced NIDCAP certified developmental specialists, and superb nursing and neonatology leadership, but also extensive expertise for the supervision, assurance, and bias-free measurement of intervention implementation fidelity. Acquisition of complex databases and analysis of large data sets is often a challenge in clinical settings. The main research questions typically asked concern NIDCAP effectiveness in terms of medical, neurobehavioral, neurophysiologic, and brain structural outcome; effects on parents; long- term effectiveness; and effects on staff and systems. Some studies have investigated change processes and differential effectiveness for specific infant subgroups. All existing phase lag design and randomized NIDCAP trials have shown positive results for infants and their families; none has found any negative effects. As a whole, results provide consistent evidence for improved lung function, feeding behavior and growth, reduced length of hospitalization, as well as improved neurobehavioral, neurophysiological, and neurostructural functioning. [6-9,11,12]

System-Wide Implementation of NIDCAP Model NICU Care

The NIDCAP approach saves significantly on NICU and later education system costs, aside from assuring significantly better quality of life for infants and their families. NIDCAP training requires significant up-front financial and time investment. Nevertheless, it is highly cost effective. Documented US care cost reductions range from of US $4,000 - $12,000 per infant. Infants are released from the requirement of intensive (Level-3) care to lower intensity (Level II) care in significantly fewer days, which measurably saves on hospital cost in any health care system. [5,85]

In order to achieve the results published in the literature, a team consisting of at least two NIDCAP certified developmental specialists, a medical and a developmental professional, guides the care as tested in the various studies. Written documentation, discussion, and guidance to families and caregivers in support of the infants' strengths and reduction of stress derives from detailed weekly bedside observations. Daily problem solving leads to environmental and care modifications geared to enhance infants and families' unique strengths and reduce vulnerabilities. The main ingredients of the intervention's success lie in the reliable daily support of the developmental specialists. Research has shown that in order to effect reliable behavior change in caregivers when in action, it is critical to provide on-site one-on-one coaching, collaboration, and guidance. Lecture and classroom ‘in-service’ practice alone result at best in knowledge change for some. Under the stress of the daily work environment, and confronted with interactive decision making, it is difficult for most adults to implement intended behavior change.[86-88] The developmental specialists’ daily support coupled with weekly up-to-date developmental care observations and recommendations, assure steady small increments of progress in the infants’ emerging strengths. Such guided care and support at the bedside guards against even minor setbacks. Setback in NICUs is often due to misinformation and miscommunication concerning the infants’ current sensitivities and reactions. The NIDCAP approach provides a framework of continued attunement and awareness of each infant’s individual trajectory in the context of the infant’s family system. Given the encouraging results of the NIDCAP studies, it behooves those responsible for NICU care to be knowledgeable and well educated in the NIDCAP model. Introduction of NIDCAP into a system involves considerable investments at all levels of organization. As mentioned earlier, it may require physical changes and adaptations. Foremost it will require substantive educational efforts and changes in the practice and leadership focus of care. The formally established international NIDCAP teaching and training program focuses on such education and provides on-site consultation towards institutional change, leadership, and reflective process capacity, while also providing formal training to those, who will be responsible for the system integration of developmental care skills and practice at the daily level. NIDCAP requires development in professional self-awareness and capacity to be present in the moment, to “hold” complex relationships and interactions. The developmentally skilled NICU professional combines highest technical skill with highest relationship skill. Figure 15 shows the conceptualization of a well-supported system.

Figure 15

The results of the studies are orderly, and consistent with the underlying conceptual basis of the individualized brain-based developmental approach described. The NIDCAP approach views infants as active participants and structures of their development who seek ongoing regulatory support during initial stabilization and continuing developmental progression. Individualized care provided by the infants' parents in collaboration with their nursery care teams and supported by a NIDCAP trained developmental specialist team may provide an extrauterine environment that supports cortical and therefore cognitive, emotional, and social-interactive development. Preterm births trigger the premature onset of sensitive periods. Preterm infants, who receive care delivered in accordance with their own goals, i.e. NIDCAP care, show much improved functioning. This appears due to the individually attuned, co-regulatory, relationship-based, and ongoing integrated incorporation of all the extrauterine sensory experiences entailed in living in a NICU, and bringing them into closer alignment with the expectations of the rapidly developing brain. All NICU work involves human interaction at many levels and at the complex interface of physical and emotional vulnerability. At its core are the tiny, immature, fully dependent, highly sensitive, and rapidly developing fetal infant and this infant's hopeful, open, and vulnerable parents, who count on and trust the caregivers' attention and investment. Therein lays the challenge and the opportunity of developmental NICU care.[89]

NIDCAP Training and the NIDCAP Federation International (NFI)

The detailed, comprehensive NIDCAP training and consultation framework developed by the NIDCAP model's originators has proven successful in equipping NICUs in many settings to bring about the change in care the NIDCAP model entails. The training involves on-site visits and consultations by trained and certified NIDCAP trainers made available to the NICU leadership teams who seek change. It entails furthermore in depth training in observation, care modification, and guidance to the staff and the designated developmental leadership core team. This core team of developmental specialists must be interdisciplinary in constituency. Its members must possess emotional maturity, self-knowledge and differentiation, interactive skill, generosity and warmth, skill as educators, role models, leaders, and change agents, and they must have the assurance of secure, full-time, developmental care staff-positions upon completion of the training process. Training typically involves a minimum of three one-week-long on-site visits by the certified NIDCAP Trainer. Training includes at each visit in-depth site consultation to the NICU leadership. In-depth independent study performed by each of the members of the interdisciplinary NIDCAP leadership team in training occurs under the guidance of and with critical feedback from the NIDCAP Trainer. The NIDCAP Trainer furthermore guides and critically evaluates on-site performance by the professionals involved in the training. At a level of basic NIDCAP proficiency, the trainer evaluates the trainee in preparation for the first phase of clinical implementation, the Advanced Practicum (AP). The trainer continues to provide off-site supervision and guidance to trainees in the course of the AP. The goal of the AP is the trainee's skill development in organizing and supporting the best developmentally supportive care for the selected AP infant and the infant's family from admission to the NICU, or the antenatal period, should the mother be hospitalized antenatally, to the infant's discharge home. The AP's last formal observation must be conducted at the infant's home. The AP typically reveals a nursery's consistency or relative fragmentation of care delivery, when experienced, focused on from an individual infant's, and family's perspective. The AP highlights the strengths of a nursery and points out the often-considerable discontinuities, miscommunications, and hardships for infants, families, and staff in caring for the infant. It provides many opportunities for reflection and improvement planning of care at a system's level. This makes it so important that all NIDCAP training is securely anchored at the leadership level of the NICU, and goes well beyond individual staff members' improvement of their own care practices.

Training to certification as NIDCAP professional is typically a two-year process; site change requires typically a minimum of three to five years. At this point there over 1,000 certified NIDCAP professional internationally. Training and system change requires the reliable availability of continued reflective process consultation work by a professional skilled in adult professional and system change guidance. Such professionals may be psychologists, psychiatrists, professional personnel counselors and others. They are best contracted for the specific nursery system from outside the system in order to establish more readily the trust of the different disciplines in the nursery. Role ambivalence and conflict must be avoided if delicate and deep-seated systems and professional issues are to be brought to the fore in order to be reframed productively and developed to a higher level of competence. Professional groups, physicians, nurses, managers, directors etc may require separate reflective process consultants until trust relationships are well developed. Time for such work, reflective group work, and the option for individual professional reflective work, must be set aside in the work schedule of the typically already overstretched professionals, if developmental care implementation is to take hold, grow, and flourish. [90-92]

Since the first publications and utilization of the NIDCAP approach, training of professionals has increased dramatically. In order to fulfill the growing training demand, the originators of the NIDCAP training approach (Heidelise Als, PhD psychologist, and her collaborators gretchen Lawhon, RN, PhD, Rita Gibes, RN MSN, and Elizabeth Browne, MD) established the first NIDCAP training center, the National NIDCAP Training Center at the Children's Hospital Boston and the Brigham and Women's Hospital in Boston, in 1984. The second training center was established at the University of Oklahoma Medical Center in 1986. Since then sixteen NIDCAP Training Centers have been established, nine in the United States of America, six in Europe (Sweden, France, two in the Netherlands, the UK, and Belgium), and one in Argentina, South America. Additional NIDCAP Training Centers are currently in development in the US, Italy, Norway, Spain, Canada, Australia, Germany, Chile, and the Far East.

Given the great demand for training and training center development, a program for the education, training, and certification of NIDCAP Trainers was developed. These are NIDCAP professionals, who meet the requirements, and are certified to train and certify NIDCAP Professionals. Most recently, a program was developed for the education, training, and certification of NIDCAP Master Trainers, i.e. certified NIDCAP Trainers, who meet the requirements, and are certified to train NIDCAP Trainers. Need for Senior NIDCAP Master Trainers is apparent as the request for Training Center development and for Master Trainers is on the increase. NIDCAP Training Centers provide instruction for professionals in newborn care and consultation for the implementation of developmentally supportive care in NICU and SCN settings. NIDCAP Training Centers also provide training in the APIB, an important tool that each NIDCAP Trainer is required to master. The APIB avails the Trainer, who typically is the key developmental leadership professional in a NICU, with an in-depth instrument with which to assess and understand individual infants and guide their care most appropriately. The APIB furthermore provides the developmental leadership professional in a NICU with a research instrument that is appropriate to test the questions that NIDCAP and other topics involving assessment of infant competence pose. Professionals eligible and suitable for training in NIDCAP and in the APIB include neonatologists, behavioral pediatricians and pediatric NICU neurologists, psychologists, and advanced level nurses, therapists, early childhood specialists, early intervention specialists, social work professionals and special education professionals. Based on extensive experience, moving towards successful implementation of and continued growth in newborn intensive care in the NIDCAP model is typically a multi-year process, and involves a dedicated team of NICU professionals who work together towards the common goal of providing the best developmental care for the infants and families in their nurseries.

Reflective process work, as described earlier, is a key component of such training and of a well-functioning NIDCAP NICU system. More information about training is available at the NIDCAP website www.nidcap.org.

The growth and impact of NIDCAP is spreading to NICUs around the world. The work of implementation of developmental care and its research continues. In the year 2000, the community of NIDCAP Training Centers and Trainers formed the NIDCAP® Federation International (NFI), a non-profit professional membership corporation. The NFI's motto is 'Changing the future for infants in intensive care'. One of the NFI's key objectives is assurance of the quality of implementation and training of the comprehensive, dynamic, evidence and systems-based, differentiated NIDCAP approach. The NFI is the NIDCAP certifying agency. The NFI's quality standards of training and implementation help guard against simplified 'knock-off' versions of NIDCAP, which lack the theoretical foundation, thorough training, and scientific evidence. The NFI at this point has about 150 professional voting members, who uphold its by-laws and articles, and the policies adopted by its Board of Directors. All Board positions are on a volunteer basis. The officers of the NFI include a President, Vice-President, Treasurer, and Secretary, all volunteer positions as well. A part-time paid-position Executive Director and part-time Assistant Secretary at this point provide for the NFI's infrastructure. The NFI Board of eleven Directors, two of whom are NICU Family Direct written documentation, discussion, and guidance to families and caregivers in support of the infants' strengths and reduction of stress ors, has established 12 working Committees, each of which is headed by a Board Member, who draws on the expertise of other NIDCAP Professionals around the world. The Committees spearhead major NFI initiatives in order to develop further the organization and to foster best NIDCAP implementation. One important programmatic initiative currently in development is the NIDCAP Nursery Certification Program (NNCP). This program establishes the criteria of 'good enough' standards of NIDCAP care implementation on a nursery-wide level. The NNCP provides for an application process, a review and site visit process, and an educational consultive program to help nurseries achieve NIDCAP Nursery Certification. NIDCAP Nursery Certification acknowledges and declares publicly that all aspects of care in the respective NICU system meet NFI certification criteria. That means that they are measurable and have been found good enough to warrant NFI certification. At this point, the pilot process of The NNCP has begun and the first pilot nursery has successfully passed inspection and deemed qualified for certification. Two additional NICUs in the USA are preparing to serve as pilot nursery systems for the NIDCAP Nursery Certification Program, after which the NNCP is expected to be launched. Several additional nurseries have already signed up for subsequent inspection and certification.

Other committees' initiatives involve fund raising; the establishment of membership levels and policies; the development of a parent and family focus within the NFI with a family membership category, a family committee, and family component of the NFI website; the development of a fully computerized online NIDCAP training data base; and the production of a continuously updated NIDCAP relevant literature data base; among several others. The Products and Services Committee produces the biannual NIDCAP newsletter *'The Developmental Observer'*, published by the NFI and distributed in hard copy to its members, and publicly available on line.

NFI revenue derives from annual individual membership dues, training center dues, donations, and Private Foundation grants. The NFI sponsors an annual NIDCAP Trainers Meeting, which is hosted each year by one of the established NIDCAP Training Centers. Attendance is mandatory for NFI approved NIDCAP Trainers-in-Training, certified NIDCAP Trainers and Directors of NFI approved NIDCAP Training Centers-in-Development and Certified NIDCAP Training Centers. Otherwise, attendance is on invitation only: A NIDCAP Training Center Director may invite other NIDCAP professionals or specifically NIDCAP-interested persons. The Annual

Trainers Meeting serves in-depth communication and update of experience and learning for trainers and centers, and as such provides the annual minimum requirement of continuing education for all trainers.

Summary

In summary, reading and trusting the preterm infant's behavior as meaningful communication moves traditional newborn intensive care delivery into a collaborative, relationship-based neurodevelopmental framework. It leads to respect for infants and families as mutually attuned and invested in one another, and as active structurers of their own developments. It sees infants, parents, and professional caregivers engaged in continuous co-regulation with one another, and in turn with their social and physical environments. It highlights mutually supportive realization of developmentally and individually specific expectations for the increasing differentiation and modulation towards shared goals, and improved outcomes. Such an approach emphasizes from early on the infant's own strengths and developmental goals, and institutes support for the infant's self-regulatory competence and achievement of these goals. Furthermore, the individualized, developmental approach to care as defined in the NIDCAP model, improves outcome not only medically, but also behaviorally, neuro-physiologically, and in terms of brain structure. It improves parent competence and staff satisfaction, and it reduces cost in the short and long run. The NIDCAP model is based on scientific evidence. The research results indicate that increase in support to behavioral self-regulation improves developmental outcome along many dimensions. The processes involved likely entail prevention of inappropriate inputs during a highly sensitive period of brain development and fostering of the brain's receptivity and opportunity for appropriate inputs. Furthermore involved is likely the fostering of caregivers' and parents' confidence in understanding and supporting the infant as a competent individual, a fetus courageous enough to fight for survival and continuation of intrauterine development despite requiring intensive medical care. Figure 16 shows the image of a tiny infant supported by a respirator, and cared for in skin-to-skin contact by the infant's mother. Figure 17 shows a proud father holding his growing and competent daughter against his bare chest.

Figures 16 and 17

Given the encouraging results of the NIDCAP research studies, as well as the training and education efforts, it behooves those responsible for NICU care to be knowledgeable of and educated in the NIDCAP model. The introduction of NIDCAP into a medical system involves considerable investment at all levels of organization. It requires substantive educational efforts; changes in the practice of care and of professionals' role definition, as well as internal personal growth and change in each of the professionals involved in NICU systems. Reflective process work is an essential ingredient of all such change and of the assurance of continued growth. The futures of infants and families in intensive care depend on the true implementation of individualized, developmentally supportive, family centered care. As professionals, we must warrant their trust.

1. Als H, Lawhon G, Brown E, Gibes R, Duffy FH, McAnulty GB, et al. Individualized behavioral and environmental care for the very low birth weight preterm infant at high risk for bronchopulmonary dysplasia: Neonatal Intensive Care Unit and developmental outcome. *Pediatr* 1986;78:1123-1132.
2. Becker PT, Grunwald PC, Moorman J, Stuhr S. Effects of developmental care on behavioral organization in very-low-birth-weight infants. *Nurs Res* 1993;42:214-220.
3. Becker PT, Grunwald PC, Moorman J, Stuhr S. Outcomes of developmentally supportive nursing care for very low birthweight infants. *Nurs Res* 1991;40:150-155.
4. Parker SJ, Zahr LK, Cole JG, Brecht M. Outcome after developmental intervention in the neonatal intensive care unit for mothers of preterm infants with low socioeconomic status. *J Pediatr* 1992;120:780-785.

5. Petryshen P, Stevens B, Hawkins J, Stewart M. Comparing nursing costs for preterm infants receiving conventional vs. developmental care. *Nurs Econ* 1997;15:138-150.
6. Als H, Lawhon g, Duffy FH, McAnulty GB, Gibes-Grossman R, Blickman JG. Individualized developmental care for the very low birthweight preterm infant: Medical and neurofunctional effects. *JAMA* 1994;272:853-858.
7. Buehler DM, Als H, Duffy FH, McAnulty GB, Liederman J. Effectiveness of individualized developmental care for low-risk preterm infants: Behavioral and electrophysiological evidence. *Pedia* 1995;96:923-932.
8. Westrup B, Kleberg A, von Eichwald K, Stjernqvist K, Lagercrantz H. A randomized controlled trial to evaluate the effects of the Newborn Individualized Developmental Care and Assessment Program in a Swedish setting. *Pedia* 2000;105:66-72.
9. Fleisher BF, VandenBerg KA, Constantinou J, Heller C, Benitz WE, Johnson A, et al. Individualized developmental care for very-low-birth-weight premature infants. *Clin Pediatr* 1995;34:523-529.
10. Heller C, Constantinou JC, VandenBerg K, Benitz W, Fleisher BE. Sedation administered to very low birth weight premature infants. *J Perinatol* 1997;17:107-112.
11. Als H, Gilkerson L, Duffy FH, McAnulty GB, Buehler DM, VandenBerg KA, et al. A three-center randomized controlled trial of individualized developmental care for very low birth weight preterm infants: Medical, neurodevelopmental, parenting and caregiving effects. *J Dev Behav Pediatr* 2003;24:399-408.
12. Als H, Duffy FH, McAnulty GB, Rivkin MJ, Vajapeyam S, Mulkern RV, et al. Early experience alters brain function and structure. *Pedia* 2004;113:846-857.
13. Jacobs S, Sokol J, Ohlsson A. The newborn individualized developmental care and assessment program is not supported by meta-analyses of the data. *J Pediatr* 2002;140:699-706.
14. Als H, Lester BM, Tronick EZ, Brazelton TB. Towards a research instrument for the assessment of preterm infants' behavior. Fitzgerald HE, Lester BM, Yogman MW, editors. In: *Theory and Research in Behavioral Pediatrics*. New York: Plenum Press; 1982. 35-63.
15. Als H, Lester BM, Tronick EZ, Brazelton TB. Manual for the assessment of preterm infants' behavior (APIB). Fitzgerald HE, Lester BM, Yogman MW, editors. In: *Theory and Research in Behavioral Pediatrics*. New York: Plenum Press; 1982. 65-132.

16. Bayley N. *Bayley Scales of Infant Development*. New York: The Psychological Corporation; 1969.
17. Bayley N. *Bayley Scales of Infant Development, Second Edition*. San Antonio, Texas: The Psychological Corporation; 1993.
18. Kleberg A, Westrup B, Stjernqvist K. Developmental outcome, child behavior and mother-child interaction at 3 years of age following Newborn Individualized Developmental Care and Intervention Program (NIDCAP) intervention. *Early Hum Dev* 2000;60:123-135.
19. Griffiths R. *The abilities of young children*. London: Child Development Research Centre; 1970.
20. Clark R, Paulson A, Colin S. Assessment of developmental status and parent-infant relationship: The therapeutic process of evaluation,. Zeanah C, editor. In: *Handbook of Infant Mental Health*. New York: Guilford Press; 1993.
21. Westrup B, Böhm B, Lagercrantz H, K. S. Preschool outcome in children born very prematurely and cared for according to the Newborn Individualized Development Care and Assessment Program (NIDCAP). In: *Developmentally supportive neonatal care: A study of the Newborn Individualized Developmental Care and Assessment Program (NIDCAP) in Swedish settings*. Stockholm: Repro Print AB; 2003. VI:1-21.
22. Villar J, Merialdi M, Gulmezoglu AM, Abalos E, Carroli G, Kulier R, et al. Characteristics of randomized controlled trials included in systematic reviews of nutritional interventions reporting maternal morbidity, mortality, preterm delivery, intrauterine growth restriction and small for gestational age and birth weight outcomes. *Journal of Nutrition* 2003;133:1632-1639.
23. Creasy RK. Preventing preterm birth. *New England Journal of Medicine* 1991 5:669-674.
24. Savitz DA, Harlow SD. Selection of reproductive health end points for environmental risk assessment. *Environmental Health Perspective* 1991 90:150-164.
25. Lockwood CJ, Kuczynski E. Risk stratification and pathological mechanisms in preterm delivery. *Pediatric Perinatal Epidemiology* 2001 15:78-89.
26. McGrath JM. Developmentally supportive caregiving and technology in the NICU: Isolation or merger of intervention strategies? *J Perinat Neonatal Nurs* 2000;14:78-91.
27. McCormick MC. Has the prevalence of handicapped infants increased with improved survival of the very low birthweight infant? *Clin Perinatol* 1993;20:263-277.

28. Vohr BR, Wright LL, Dusick AM, Mele L, Verter J, Steichen JJ, et al. Neurodevelopmental and functional outcomes of extremely low birth weight infants in the national institute of child health and human development neonatal research network, 1993-1994. *Pedia* 2000;105:1216-1226.
29. Saigal S, Stoskopf B, Streiner D, Boyle M, Pinelli J, Paneth N, et al. Transition of Extremely Low-Birth-Weight Infants From Adolescence to Young Adulthood: Comparison with Normal Birth-Weight Controls. *Journal of the American Medical Association* 2006;295:667-675.
30. Saigal S, Hoult L, Streiner DL, Stoskopf BL, Rosenbaum PL. School difficulties at adolescence in a regional cohort of children who were extremely low birth weight. *Pedia* 2000;105:325-331.
31. Saigal S, Szatmari P, Rosenbaum P. Can learning disabilities in children, who were extremely low birth weight be identified at school entry? *Dev Beh Pediatr* 1992;13:356-362.
32. Hack M, H.G. T, Drotar D, Schluchter M, Cartar L, Andreias L, et al. Chronic conditions, functional limitations, and special health care needs of school-aged children born with extremely low-birth-weight in the 1990s. *JAMA* 2005;294:318-325.
33. Biagioni E, Bartalena L, Boldrini A, Pieri R, G. C. Electroencephalography in infants with periventricular leukomalacia: prognostic features at preterm and term age. *J Child Neurol* 2000 15:1-6.
34. Mercuri E, Barnett A, Rutherford M, Guzzetta A, Haataja L, Cioni G, et al. Neonatal cerebral infarction and neuromotor outcome at school age. *Pediatrics* 2004 113:95-100.
35. Hofer MA. Early social relationships: A psychobiologist's view. *Child Dev* 1987;58:633-647.
36. Hack M, Flanner DJ, Schluchter M, Cartar L, Borawski E, Klein N. Outcomes in young adulthood for very-low-birth-weight infants. *NEJM* 2002;346:149-157.
37. Marin-Padilla M. Pathogenesis of late-acquired leptomeningeal heterotopias and secondary cortical alterations: A golgi study. Galaburda AM, editor. In: *Dyslexia and Development.* Cambridge, Mass.: Harvard University Press; 1993. 64-89.
38. Gesell A, Armatruda C. *The Embryology of Behavior*. Westport, CT.: Connecticut Greenwood Press; 1945.
39. Humphrey T. Some correlations between the appearance of human fetal reflexes and the development of the nervous system. *Prog Brain Res* 1964;4:93-135.

40. Als H. Toward a synactive theory of development: Promise for the assessment of infant individuality. *Inf Mental Health J* 1982;3:229-243.
41. Denny-Brown D. *The Basal Ganglia and Their Relation to Disorders of Movement*. Oxford: Oxford University Press; 1962.
42. Volpe JJ. *Neurology of the Newborn, 4th Edition*. Philadelphia: WB Saunders; 2001.
43. Anand KJS, Scalzo FM. Can adverse neonatal experiences alter brain development and subsequent behavior? *Biol Neonat* 2000;77:69-82.
44. Bourgeois JP, Jastreboff PJ, Rakic P. Synaptogenesis in visual cortex of normal and preterm monkeys: Evidence for intrinsic regulation of synaptic overproduction. *Proc NA Sci* 1989;86:4297-4301.
45. Als H. The newborn communicates. *J Commun* 1977;27:66-73.
46. Grossman K. Die Wirkung des Augenoffnens von Neugeborenen auf das Verhalten ihrer Mutter. *Geburtshilfe und Frauenheilkunde* 1978;38:629-635.
47. Als H, Duffy FH. The behavior of the fetal newborn: Theoretical considerations and practical suggestions for the use of the APIB. Waldstein A, Gilderman D, Taylor-Hershel D, Prestridge S, Anderson J, editors. In: *Issues in Neonatal Care*. Chapel Hill, NC: WESTAR/TADS; 1982. 21-60.
48. Als H, Duffy FH, McAnulty GB. Neurobehavioral regulation disorder of prematurity. *IBD* 1990;13:159.
49. Als H, Duffy FH, McAnulty GB. Behavioral differences between preterm and fullterm newborns as measured with the APIB system scores: I. *IBD* 1988a;11:305-318.
50. Als H, Duffy FH, McAnulty GB. The APIB: An assessment of functional competence in preterm and fullterm newborns regardless of gestational age at birth: II. *IBD* 1988b;11:319-331.
51. Duffy FH, Als H, McAnulty GB. Behavioral and electrophysiological evidence for gestational age effects in healthy preterm and fullterm infants studied 2 weeks after expected due date. *Child Dev* 1990;61:1271-1286.
52. Mouradian L, Als H, Coster W. Neurobehavioral functioning of healthy preterm infants of varying gestational ages. *Dev Behav Peds* 2000;21:408-416.
53. Als H, Duffy FH, McAnulty GB. The APIB: An assessment of functional competence in preterm and fullterm newborns regardless of gestational age at birth: II. *IBD* 1988;11:319-331.

54. Duffy FH, Als H, McAnulty GB. Infant EEG spectral coherence data during quiet sleep: Unrestricted Principal Components Analysis - Relation of factors to gestational age, medical risk, and neurobehavioral status. *Clin Electroenceph* 2003;34:54-69.

55. Hüppi PS, Warfield S, Kikinis R, Barnes PD, Zientara GP, Jolesz FA, et al. Quantitative magnetic resonance imaging of brain development in premature and mature newborns. *Ann Neurol* 1998;43:224-235.

56. Hüppi PS, Schuknecht B, Boesch C, Bossi E, Felblinger J, Fusch C, et al. Structural and neurobehavioral delay in postnatal brain development of preterm infants. *Ped Res* 1996;39:895-901.

57. Zimine S, Lazeyras F, Henry F, Borradori-Tolsa C, Hüppi P. Study of brain development by diffusion tensor imaging: evidence of altered brain development in newborn babies with intrauterine growth restriction. *Proc Intl Soc Mag Reson Med* 2002;10.

58. Mewes AUJ, Als H, McAnulty G, Inder T, Hüppi P, Rybicki MD, et al. Regional brain development of low-risk preterm infants differs from fullterm infants. Paper presented at: 2005 Pediatric Academic Societies' Meeting; May, 2005; Washington.

59. Murphy B, Inder TE, Hüppi PS, Warfield S, Zientara GP, Kikinis R, et al. Impaired cerebral cortical gray matter growth after treatment with dexamethasone for neonatal chronic lung disease. *Pedia* 2001;107:217-221.

60. Peterson BS, Anderson AW, Ehrenkranz R, Staib LH, Tageldin M, Colson E, et al. Regional brain volumes and their later neurodevelopmental correlates in term and preterm infants. *Pedia* 2003;111:939-948.

61. Marin-Padilla M. Prenatal development of fibrous (white matter), protoplasmic (gray matter), and layer I astrocytes in the human cerebral cortex: a Golgi study. *The Journal Of Comparative Neurology* 1995;357:554-572.

62. Marin-Padilla M. Developmental neuropathology and impact of perinatal brain damage. I: Hemorrhagic lesions of neocortex. *Journal Of Neuropathology And Experimental Neurology* 1996;55:758-773.

63. Marin-Padilla M. Developmental neuropathology and impact of perinatal brain damage. II. White matter lesions of the neocortex. *J Neuropathol Exp Neurol* 1997;56:219-235.

64. Mewes A, Zöllei L, Hüppi P, Als H, McAnulty G, Inder T, et al. Displacement of brain regions in preterm infants with non-synostotic dolichocephaly investigated by MRI. *J Neuroimag* in press.

65. Hutchison BL, Hutchison LA, Thompson JM, Mitchell EA. Plagiocephaly and brachycephaly in the first two years of life: a prospective cohort study. *Pediatrics* 2004:970-980.
66. Hutchison L, Stewart A, Mitchell E. Infant sleep position, head shape concerns, and sleep positioning devices *Journal of Paediatrics and Child Health* 2007;43:243-248.
67. Carlan SJ, Wyble L, Lense J, Mastrogiannis DS, Parsons MT. Fetal head molding. Diagnosis by ultrasound and a review of the literature. *Journal of Perinatology: Official Journal of the California Perinatal Association* 1991;11:105-111.
68. C.C. H, Liu CC. The differences in growth of cerebellar vermis between appropriate-for-gestational-age and small-for-gestational-age newborns. *Early Hum Dev* 1993;33:9-19.
69. Mewes AUJ, Hüppi PS, Als H, Rybicki FJ, Inder TE, McAnulty GB, et al. Regional brain development in serial MRI of low-risk preterm infants. *Pedia* 2006;118:23-33.
70. Huttenlocher PR, Dabholkar AS. Regional differences in synaptogenesis in human cerebral cortex. *The Journal of Comparative Neurology* 1997;387:167-178.
71. Bourgeois JP, Goldman-Rakic PS, Rakic P. Synaptogenesis in the prefrontal cortex of rhesus monkeys. *Cerebral Cortex (New York, NY: 1991)* 1994;4:78-96.
72. Rakic P, Bourgeois JP, Eckenhoff MF, Zecevic N, Goldman-Rakic PS. Concurrent overproduction of synapses in diverse regions of primate cerebral cortex. *Science* 1986;232:231-235.
73. Stewart A, Kirkbride V. Very preterm infants at fourteen years: relationship with neonatal ultrasound brain scans and neurodevelopmental status at one year. *Acta Paediatr Suppl* 1996;416:44-47.
74. Stewart AL, Rifkin L, Amess PN, Kirkbride V, Townsend JP, Miller DH. Brain structure and neurocognitive and behavioral function in adolescents who were born very preterm. *Lancet* 1999;353:1653-1657.
75. Rushe T, Rifkin L, Stewart AL, Townsend J, Roth S, Wyatt J, et al. Neuropsychological outcome at adolescence of very preterm birth and its relation to brain structure. *Dev Med & Child Neurol* 2001;43:226-233.
76. Mercuri E, Jongmans M, Henderson S, Pennock J, Chung YL, de Vries L, et al. Evaluation of the corpus callosum in clumsy children born prematurely: a functional and morphological study. *Neuropediatrics* 1996;27:317-322.

77. Peterson BS, Vohr B, Staib LH, Cannistraci CJ, Dolberg A, Schneider KC, et al. Regional brain volume abnormalities and long-term cognitive outcome in preterm infants. *JAMA* 2000;284:1939-1947.

78. Allin M, Matsumoto H, Santhouse AM, Nosarti C, AlAsady MHS, Stewart AL, et al. Cognitive and motor function and the size of the cerebellum in adolescents born very preterm. *Brain* 2001;124:60-66.

79. Als H. A synactive model of neonatal behavioral organization: Framework for the assessment and support of the neurobehavioral development of the premature infant and his parents in the environment of the neonatal intensive care unit. *Phys and Occup Ther Pediatrics* 1986;6:3-53.

80. Als H, Butler S, Kosta S, McAnulty G. The assessment of preterm infants' behavior (APIB): Furthering the understanding and measurement of neurodevelopmental competence in preterm and fullterm infants. *Ment Retard & Develop Disab Res Rev* 2005;11:94-102.

81. Als H. Program Guide - Newborn Individualized Developmental Care and Assessment Program (NIDCAP): An Education and Training Program for Health Care Professionals. Boston: Children's Medical Center Corporation; 1986 rev 2006.

82. Als H. Reading the premature infant. Goldson E, editor. In: *Developmental Interventions in the Neonatal Intensive Care Nursery*. New York: Oxford University Press; 1999. 18-85.

83. Als H. Manual for the naturalistic observation of the newborn (preterm and fullterm). Boston: Children's Hospital; 1981, rev. 1995.

84. Als H, Butler S. Neurobehavioral development of the preterm infant. Martin R, Fanaroff A, Walsh M, editors. In: *Fanaroff and Martin's Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant*. 8th ed. St. Louis: Mosby; 2005. 1051-1068.

85. Stevens B, Petryshen P, Hawkins J, Smith B, Taylor P. Developmental versus conventional care: A comparison of clinical outcomes for very low birth weight infants. *Canadian J Nurs Res* 1996;28:97-113.

86. Joyce B, Showers B. *Student achievement through staff development* 3rd ed. Alexandria, VA: ASCD; 2002.

87. Fixsen DL, Naoom SF, Blase KA, Friedman RM, Wallace F. Implementation research: A synthesis of the literature. Tampa, FL: University of South Florida: Louis de la Parte Florida Mental Health Institute, The National Implementation Research Network; 2005.

88. Fixsen DL, Blase KA, Naoom SF, Wallace F. Evidence-based education to benefit students and society. Tampa, FL: University of South Florida: Louis de la Parte Florida Mental Health Institute, The National Implementation Research Network; 2007.

89. Als H. Individualized, family-focused developmental care for the very low birthweight preterm infant in the NICU. Friedman SL, Sigman MD, editors. In: *Advances in Applied Developmental Psychology*. Norwood, NJ: Ablex Publishing Company; 1992. 341-388.

90. Gilkerson L. Understanding institutional functioning style: A resource for hospital and early intervention collaboration. *Inf Young Children* 1990;2:22-30.

91. Gilkerson L, Als H. Role of reflective process in the implementation of developmentally supportive care in the newborn intensive care unit. *Inf Young Child* 1995;7:20-28.

92. Als H, Gilkerson L. Developmentally supportive care in the neonatal intensive care unit. *Zero to Three* 1995;15:1-10.