CHAPTER 6

Early Nutritional Deficiencies in Brain Development: Implications for Psychopathology

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The influence of early nutrition on the developing brain has been an issue that has waxed and waned in scientific popularity over the past century (Susser & Stein, 1994). However, popular culture has recognized the importance of early nutrition in children's health for many years. The Nobel Prize-winning author Pearl S. Buck wrote about the devastating effects of starvation on young children in her 1931 classic book The Good Earth. In this novel, the first daughter of the main character is born at the height of a severe famine. Buck implies that the significant malnutrition the child endured early in life resulted in devastating brain damage, leaving her profoundly retarded.

Conditions such as phenylketonuria (PKU) illustrate the importance of nutritional factors in brain development. If not addressed, PKU can result in mental retardation (Huttenlocher, 2000; Sullivan & Chang, 1999). Individuals with PKU are unable to metabolize phenylalanine; the subsequent buildup of this amino acid during brain development results in a toxic reaction leading to brain damage (Huttenlocher, 2000). Reports hypothesizing a nutritional origin of some forms of mental retardation first appeared in the early 1950s, when researchers noted high amounts of phenylketones in the urine of some mentally retarded individuals (Huttenlocher, 2000). Subsequent investigations linked PKU to various neuropathologies, including diffuse white matter changes and reduced dendritic branching (Huttenlocher, 2000). Specific genetic disorders resulting in deficiencies of micronutrients (such as copper in Menkes disease), regional geographic deficiencies of trace elements (such as iodine and selenium), and low prenatal levels of maternal nutrients (such as folate and iron) have all been linked to severe neurological abnormalities and/or intellectual deficits (Hibbard & Smithells, 1965; Lozoff, 1989; Pharoah, Buttfield, & Hetzel, 1971; Prohaska, 2000; Shim & Harris, 2003; Yi-Ming, 1996).

The famines and food shortages throughout Europe during the Second World War created an interest in studying the changes in psychological and physiological functioning caused by undernutrition (Keys, 1946; Pollitt, 1988). Although much of this research pertains to adults, it is pertinent here because children likely exhibit similar psychological consequences and, by affecting the psychological state of their caregivers, parental malnutrition may exert indirect effects on children regardless of their nutritional status (Brozek, 1990).

Keys and colleagues at the University of Minnesota exposed 36 healthy males to 6 months of semistarvation followed by 3 months of controlled rehabilitation (Franklin, Schiele, Brozek, & Keys, 1948; Keys, 1946). Results indicated that during the period of semistarvation, the participants became lethargic, apathetic, less sociable, uninterested in sexual activity, less alert (except with regard to hearing), and depressed. Although the participants complained about changes in mental alertness and inability to think cogently, researchers noted no decreases on tests of memory or intellectual ability. The participants in the study exhibited unusual behaviors involving food, such as compulsive gum chewing and coffee/tea drinking (up to 40 packs...
of gum a day and 15 cups of coffee a day), “souping” (the practice of drinking the liquid in soup then refilling the bowl with hot salted water and repeating the process before eating the vegetables in the soup), and unusual eating habits, including novel spice concoctions, hoarding of food, and doting over every last piece of food on the plate. Many of the participants greatly increased their daily consumption of water and either began smoking or substantially increased the amount they smoked (Franklin et al., 1948). Finally, participants displayed numerous physiological reactions, such as decreased sensitivity to heat, increased sensitivity to cold, edema, skin discoloration, and reduced hair growth (Franklin et al., 1948).

During the controlled rehabilitation phase, participants were initially irritable and easily frustrated (Franklin et al., 1948). These effects were short-lived; however, weight gain and sexual interest did not immediately return to prestarvation levels. In fact, participants did not reach their prestarvation weight and level of physical fitness until almost a year after the conclusion of the semistarvation phase (Franklin et al., 1948).

These findings are important because they indicate that periods of substantial undernutrition in adults result in demonstrable (but reversible) alterations in behavior, physiology, and mood (Franklin et al., 1948; Keys, 1946). The reversibility of these symptoms suggests that, in adults, behavioral changes occur secondarily to disturbances in neurotransmitter systems. This conjecture is supported by work (with humans and animals) showing dietary manipulations resulting in rapid changes in behavior and concentration of specific neurotransmitters (Fromentin, Gietzen, & Nicolaidis, 1997; Gietzen & Magrum, 2001; Phillips, Oxtoby, Langley, Bradshaw, & Szabadi, 2000; Riedel, 2004; Pierucci-Lagha et al., 2004). In the developing brain, the effects of undernutrition may not be as amenable to rehabilitation because this condition likely impacts both neurotransmitter systems and neuroanatomic organization (Winick & Rosso, 1969).

Using a natural experiment, Stein, Susser, Saenger, and Marolla. (1972) investigated whether prenatal exposure to famine in the Dutch “hunger winter” of 1944 to 1945 adversely affected intellectual abilities in a sample of 19-year-old males. In September 1944, the Netherlands cooperated with Allied forces in an attempt by British paratroopers to force a bridgehead over the Rhine River (Stein et al., 1972, 1975; Susser, Brown, Klonowski, Allen, & Lindenbaum, 1998). The attempt failed, and in retaliation, the German army imposed a trade embargo on Holland. Unfortunately, even when the army lifted the embargo, previous railroad strikes and a severe winter that had frozen the shipping channels resulted in serious food shortages in much of western Holland. At the height of the famine, daily food rations could be as low as 450 kilocalories per person, a quarter of the standard amount. The most significant period of the famine began in November 1944 and lasted until Allied armies crossed the Rhine and liberated Holland in May 1945. The severity of famine was indicated by a sharply increased death rate in the affected cities (many of these deaths were attributed to starvation), substantial (up to 25%) loss in body weight, and the occurrence of physical signs associated with severe malnourishment, such as osteomalacia and hunger edema (Stein et al., 1972, 1975).

This event was unique because it occurred at a specified time and place in a population that before and after famine had good nutrition, there was good reporting on food rations provided to the population, and excellent public health records allowed researchers to divide individuals into groups of varying exposures based on birth date and birth location. This natural experiment has generated numerous investigations on the effects of prenatal famine exposure on a multitude of psychological and medical variables.

Stein et al. (1972) grouped individuals into six birth cohorts based on their intrauterine exposure to famine: individuals born before the beginning of the famine, individuals prenatally exposed to famine in the third trimester only, individuals exposed to famine in the middle 6 months of gestation, individuals conceived during the famine and exposed in the first and second trimesters, individuals conceived during the famine and exposed during the third trimester only, and individuals conceived and born after the famine occurred. Stein and colleagues used Raven Progressive Matrices scores gathered at age 19 during military induction testing to compare these cohorts to control cohorts born during the same time frame in cities of similar size but not affected by the famine. The researchers failed to find significant declines in average IQ or increases in the rates of mild or severe mental retardation in the four groups prenatally exposed or in the one group exposed postnatally. Because many births occurred at home, the researchers could not evaluate the influence of prenatal famine exposure on the birthweight of the entire cohort; however, a subsample of births occurring in hospitals in the famine and control cities indicated no relationship of birthweight to IQ at age 19.

These findings cast doubt on the assertion that maternal malnutrition alone results in significantly lower intellectual abilities. However, the authors emphasize that their findings should not be generalized to chronically malnourished populations where the mother is likely to be malnourished before and after parturition, the child is at high risk
for postnatal nutritional deficits, or deficiencies in specific trace nutrients are common. The authors suggest that their findings reveal either a high degree of protection afforded to the developing child in utero or the considerable resilience of many children in the face of prenatal insult.

Over the years, many people have speculated that nutrition affects proximal behavior (e.g., sugar increases activity levels). Although careful research has not substantiated this particular assertion, there are many clearly documented short-term effects of specific nutrients (or substances) on behavior (Beyth & Baratta, 1996; Fernstrom, 2000; Fishbein & Pease, 1994; Lieberman, 2003). However, these acute effects are not the topic of this chapter. Rather, the discussion focuses on the effects of generalized malnutrition or specific micronutrient deficiencies on the developing brain and how these insults may contribute to the later emergence of psychopathology.

Before beginning the discussion in earnest, it is important to define several terms. First, in this chapter, early undernutrition refers to caloric restriction occurring prenatally (sometimes even prior to conception) or in the first few years of postnatal development (prior to age 3). Second, undernutrition or malnutrition (used interchangeably throughout) refers to a general reduction in caloric intake, also known as protein energy malnutrition (PEM) or macronutrient malnutrition. Nutritional deficits can refer to either PEM or deficits in specific micronutrients such as iron (Fe), Zinc (Zn), or iodine (I). Most of the extant research concerns PEM/undernutrition, and this is the focus of the first section of this chapter; each of these three micronutrients is briefly discussed near the end of the chapter.

An unambiguous definition of what constitutes psychopathology has proven elusive (Lilienfeld & Marino, 1999; Meehl, 1979; Wakefield, 1993, 1999) but is not necessary here. We refer to major mental disorders as listed in the American Psychiatric Association’s (2000) Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV-TR) as constituting a large subset of psychopathology pertinent to this discussion. Most research relevant to this issue examines Schizophrenia/Schizophrenia Spectrum Disorders, internalizing disorders (such as major depression and anxiety disorders), and externalizing problems (such as Attention-Deficit/Hyperactivity Disorder [ADHD] and Antisocial Personality Disorder).

**BASIC PRINCIPLES**

When examining the effects of nutritional deficiencies on the developing brain and the role these may play in the generation of psychopathology, it is important to keep in mind several core principles. First, brain development occurs in overlapping but dissociable stages, and each of these stages may be uniquely vulnerable to injury (Honig, Herman, & Shatz, 1996; Monk, Webb, & Nelson, 2001; Morgane et al., 1993; Teicher, Andersen, Polcari, Anderson, & Navalta, 2002; Webb, Monk, & Nelson, 2001). These stages include neurulation, neurogenesis, proliferation, migration, differentiation, synaptogenesis, myelination, apoptosis, and synaptic pruning (Andersen, 2003; Monk et al., 2001; Webb et al., 2001). Disturbances in some of these processes are associated with neurobehavioral deficits—as in the nonverbal impairments and psychiatric symptoms seen in the leukodystrophies—or the hypothesis that aberrant synaptic connections play a role in the etiology of Autism and Schizophrenia (Innocenti, Ansermet, & Parnas, 2003; Keller & Persico, 2003; Percy & Rutledge, 2001; Rosebush, Garside, Levinson, & Mazurek, 1999; Van Gool, Assies, Wanders, & Barth, 1997).

Some of the initial processes of brain development (e.g., neurulation and neurogenesis) occur during a single early period, whereas other, later stages (e.g., myelination, apoptosis, and synaptic pruning) occur independently at different times in various brain regions (Monk et al., 2001; Webb et al., 2001). Thus, a brain structure/region will have its own individual course through which development proceeds. Moreover, certain brain regions such as the hippocampus are more vulnerable to injury than other regions (Walsh & Emerich, 1988). Ultimately, the result of any insult to the developing brain depends on the time of onset of the insult and what developmental processes are occurring/brain structures are actively developing at that time, how inevitably vulnerable these processes/structures are to injury, and the magnitude of the insult (e.g., the severity and/or duration of the injury). Based on these variables, a particular deficiency can have different effects on the developing nervous system (Adams et al., 2000; Georgieff & Rao, 2001; Kretchmer, Beard, and Carlson, 1996; Morgane et al., 1993; Pollitt, 1996).

A second important principle underlying the current discussion is the concept that abnormal behavior (as in psychopathology) is the effector of brain activity, and changes in neuroanatomy, neurochemistry, and neurophysiology can result in alterations in behavior (Brower & Price, 2001; Moffitt, 1993; Moffitt & Caspi, 2001; Nestor, Kimble, Berman, & Haycock, 2002; Pennington & Ozonoff, 1996; Raine, 2002). Thus, early malnutrition may lead to the expression of cognitive deficits and/or abnormal behavior stemming from alterations in fine neuroanatomy (delicate structures such as dendritic arbors and...
white matter tracks), neurochemistry (disturbances in neurotransmitter systems), and/or neurophysiology (the functioning of ion channels and specific receptors; Arnold, 1999; Benes & Berretta, 2001; Bowley, Drevets, Öngür, & Price, 2002; Konradi & Heckers, 2003; Molnar, Potkin, Bunney, & Jones, 2003). Although specific findings (e.g., white matter abnormalities or increased receptor density in a certain region) are sometimes difficult to replicate in new samples, disturbances in these three broad domains are consistently associated with various forms of psychopathology (Dwork, 1997; Fletcher, 1998; Jones, 1997).

The last core principle running through this discussion is the concept that genes will likely prove to be the single most important long-term determinant of behavior; however, their expression can be modified (repressed or activated) by interaction with the environment (Bunney et al., 2003; Jacobs et al., 2002; Murphy et al., 2001; Rutter, Pickles, Murray, & Eaves, 2001; Rutter & Silberg, 2002; Slutsker et al., 1997). Environmental influences causing anomalous neurological development (such as chronic and severe neglect or toxicity) can have especially salient and long-term effects (Barone, Das, Lassiter, & White, 2000; Castle et al., 1999; Schettler, 2001; Weiss, 2000). Similarly, nutrition is an important environmental factor that can affect the developing brain (Georgieff & Rao, 2001; Morgane et al., 1993; Morgane, Mokler, & Galler, 2002).

This does not imply that environmental insults such as malnutrition have uniform effects on people of differing genetic characteristics. It is plausible that individual differences in the capacity to maintain homeostasis in response to challenges (thereby allowing for reasonably normal development) and in—at present—poorly explicated concepts such as neurological integrity, plasticity, and resilience are genetically or experientially determined; such factors likely modulate the effects of environmental challenges such as undernutrition (Bhutta & Anand, 2002; Engle, Castle, & Menon, 1996; Morgane et al., 1993; Nelson, 2000; Sapolsky, 2001).

Furthermore, it is rarely the case that undernutrition exists independently of other risk factors such as maternal stress, genetic predisposition, poverty, and dangerous living conditions (e.g., poor sanitation or the presence of toxins such as lead; Guesry, 1998; Pollitt, 1969; Schettler, 2001; Snodgrass, 1994; Stein & Susser, 1985; Tanner & Finn-Stevenson, 2002; Trope, Lopez-Villegas, Cecil, & Lenkinski, 2001). Pollitt reported that in developing countries, children with the greatest nutritional deficits had the poorest living conditions (i.e., lack of running water or adequate plumbing, cramped housing, and large families). Thus, malnutrition may generally exert its effects by acting in concert (additively or synergistically) with other risk factors (Guesry, 1998; Morgane et al., 1993, 2002; Stein & Susser, 1985; Zeskind & Ramey, 1981). For example, Caspi and coworkers (2002) found that abused children with a genotype leading to higher levels of a neurotransmitter-metabolizing enzyme (monoamine oxidase) displayed lower rates of antisocial behavior. The authors interpreted these findings to be evidence of a gene-environment interaction in which the genotype influenced an individual’s response to a particular environmental stimulus. It is possible that analogous mechanisms or interactions could be at work in determining the outcome of early malnutrition.

**OVERVIEW**

The current chapter endeavors to examine the effect of early nutritional deficits on brain development and the role this may play in the emergence of psychopathology. We begin the discussion by examining the possible link between early nutritional insults and the development of psychopathology in the context of those studies that have specifically researched this question. After this, we step back and delve into investigations that look at the effects of early malnutrition on broader issues such as cognitive development in humans and developmental neurobiology. These factors are important because they characterize a developmental path (resulting from early malnutrition) in which psychopathology may exist as part of the milieu or which may increase an individual’s risk for the later development of mental illness. The chapter concludes with a brief hypothetical discussion of potential causal mechanisms that may account for the relationship between early nutritional insults and the later development of psychopathology.

**STUDIES ON PSYCHOPATHOLOGY**

Studies in this section are presented with regard to the spectrum of psychopathology they examine. Thus, although research in this area is sparse, studies investigating the effects of early malnutrition on Schizophrenia or Schizophrenia Spectrum Disorders, externalizing disorders (e.g., ADHD, conduct problems, and antisocial behavior), and internalizing disorders (such as depression) are discussed. In addition to other researchers, Krueger and colleagues (Krueger, 2002; Krueger, Caspi, Moffitt, & Silva, 1998; Krueger, McGue, & Iacono, 2001) have proposed the broad dimensions of externalizing and internalizing to capture more accurately the structure of common mental disorders.
These dimensions are used in the current discussion for clarity and succinctness.

Despite numerous investigations into the cognitive effects of malnutrition on children, most of the research dealing with the effects of malnutrition on the development of psychopathology concerns individuals older than 18 years. This is a significant shortcoming in our knowledge in this area because many psychiatric disorders will likely prove to have developmental origins. Thus, it is probable that these conditions have perceptible manifestations during childhood and adolescence. Similarly, early malnutrition may influence the developmental course (e.g., age of onset, severity, or progression) of psychiatric disorders. Moreover, malnutrition may be expected to exert more powerful immediate effects on the developing brain—thereby suggesting the effects of malnutrition may be more salient in individuals younger than 18. Thus, children affected by early nutritional deficits may display additional or significantly different behavioral effects than mature adults (Keys, 1946). Furthermore, it is possible that some of the cognitive manifestations of undernutrition (discussed later) may have resulted from impairments secondary to various psychiatric symptoms such as inattention or anxiety.

Much of the information regarding the relationship between early malnutrition and later psychopathology comes from data collected on cohorts prenatally exposed to famine during the Dutch hunger winter of 1944 to 1945 (A. S. Brown et al., 1996; Butler, Susser, Brown, Kaufmann, & Gorman, 1994; Hoek, Brown, & Susser, 1998; Susser, Hoek, & Brown, 1998). As discussed previously, Stein et al. (1972) found no evidence suggesting decreased intellectual abilities or increased rates of severe or mild mental retardation following prenatal famine exposure. However, years later, E. Susser (the son of the original investigators) and his collaborators revisited the famine data to examine if individuals with a history of prenatal famine exposure exhibited higher rates of psychopathology in adulthood (A. S. Brown, Cohen, Greenwald, & Susser, 2000; A. S. Brown, Susser, Lin, Neugebauer, & Gorman, 1995; Hulshoff Pol et al., 2000; Neugebauer, Hoek, & Susser, 1999; Susser & Lin, 1992; Susser et al., 1996).

Several major admonitions regarding this natural experiment should be pointed out. First, the amount of food redistribution in families is not known (Stein et al., 1972). Thus, pregnant women who occasionally received greater rations might have been supplied more calories via sacrifice of other family members (Stein et al., 1972, 1975). Second, although probably not substantially significant, it is not known how much individuals supplemented their diets with material such as tulip bulbs, which may have actually contained toxins (Stein et al., 1972, 1975). Third, these data represent a circumscribed episode of malnutrition with a previously well-nourished population who returned to this status following the famine. Therefore, these results should not be generalized to chronically malnourished populations—especially those with other substantial risk factors (Stein et al., 1972). Fourth, except for records indicating profession of father, there is no information regarding familial background. Finally, because many of the births occurred at home, it is impossible to gather information on birth or gestational complications, which, along with maternal infection and stress, may play etiological roles in the emergence of behavioral deficits and psychopathological conditions (Anand & Scalzo, 2000; A. S. Brown et al., 2000; Brown & Susser, 2002; McNeil, Cantor-Graae, & Weinberger, 2000; Teicher et al., 2002). Regardless of these essentially unavoidable imperfections, the studies discussed here provide valuable insights regarding the possible role of prenatal malnutrition in the emergence of later psychiatric disorders.

In an initial 1992 study, Susser and Lin found that women, but not men, exhibited an increased prevalence of Schizophrenia following prenatal exposure to famine in the first trimester. However, they obtained these results through a broad inclusion criterion (i.e., first trimester of gestation during periods of low food rations) and review of admission records to psychiatric hospital units from 1978 to 1989. Thus, they based exposure on a single criterion that may not have completely captured children who experienced the highest levels of exposure. Furthermore, individuals were at least 32 years old at the start of the review period. This age tends to be past the age that most males have their first psychotic episode; therefore, it is likely many men would have already made initial psychiatric contact prior to this age and were not rehospitalized during the review period (Brown et al., 1996).

In a more extensive follow-up investigation, Susser et al. (1996) used stringent inclusion criteria to define a "maximal exposure" cohort. The inclusion criteria for the other cohorts were the same as in the 1992 study. However, they defined the maximal exposure cohort to include only those individuals conceived at the height of the famine. This cohort consisted of individuals born when the general population exhibited increases in adverse health effects and new births demonstrated excess congenital malformations (which, according to Stein et al., 1973, are associated with severe prenatal starvation). These criteria ensured that the researchers dealt exclusively with the maximally exposed cohort (e.g., the cohort that underwent the most significant
early insult due to the famine). These restrictions led to the identification of a cohort born between October 15, 1945, and December 31, 1945 (Hoek et al., 1996, 1998; Susser, Hoek, et al., 1998). The authors extended the period of record review back to 1970, thereby more accurately reflecting lifetime history of psychiatric admission.

Based on these data, the researchers found a significantly increased prevalence of Schizophrenia in both males and females of the maximal exposure cohort. This cohort displayed a prevalence rate for Schizophrenia nearly 2 times higher than that of the unexposed cohort. Further, the other exposed cohorts did not differ in prevalence rate from the unexposed cohort. Susser et al. (1996) demonstrated these findings using a "narrow" and a "broad" diagnostic definition of Schizophrenia. Individuals in the maximal exposure cohort had a mother malnourished during the peri-conceptional phase, and their prenatal famine exposure occurred early in pregnancy, generally entirely within the first trimester.

Using magnetic resonance imaging, Hulshoff Pol and colleagues (2000) found increased brain abnormalities (specifically, focal white matter hyperintensities) in a subgroup of individuals from the maximal exposure cohort. They showed that individuals from this cohort diagnosed with Schizophrenia evidenced reduced intracranial volume compared to nonexposed individuals with Schizophrenia and nondiagnosed individuals with the same level of famine exposure. The authors speculated that the decreased intracranial volumes observed only in the famine-exposed individuals with Schizophrenia resulted from an interaction between genetic risk factors and early brain stunting caused by gestational malnutrition, eventually resulting in the development of Schizophrenia. They concluded that exposure to famine early in gestation is associated with increased focal brain abnormalities, possibly secondary to specific micronutrient deficiencies. In some individuals, these aberrations may result in a higher risk for developing Schizophrenia. The researchers urge discretion when examining their findings, stressing that they obtained the results using a limited number of participants and that other confounding factors could not be completely taken into account. Nevertheless, these data provide an initial glimpse into specific structural brain changes present following severe first trimester malnutrition.

Another study by the same group expanded their inquiry to determine if males conceived at the height of the hunger winter evidenced increased prevalence of schizophrenia spectrum personality disorders (SSPD) as defined by the International Classification of Diseases 6 (ICD-6; Hoek et al., 1996). This study used methodology similar to the earlier study. Thus, the authors compared the maximal exposure cohort (see Susser et al., 1996, for a description of this cohort) to an unexposed cohort and a cohort with first trimester exposure but without maternal malnutrition at the time of conception. The authors obtained data regarding the diagnosis of SSPD from military induction records; thus, males only are represented.

The investigators found that, when compared to the other groups, the maximal exposure group demonstrated a higher prevalence of SSPDs. This increase appeared to be unique to SSPDs because the three groups did not differ from one another in the prevalence of psychoneurosis, that is, general anxiety. They noted that this relationship remains consistent when estimated socioeconomic status (SES) is taken into account. However, the authors hasten to point out that despite the increased risk in the maximal exposure group, relatively few individuals in the entire study actually met criteria for SSPD. Furthermore, they cautioned that despite the apparent care taken in making these diagnoses, no formalized diagnostic system existed at the time of these evaluations. To some extent, this caution should be applied to both of the studies previously discussed.

Using information obtained from birth and medical records in a population-based cohort born between 1924 and 1932 in Helsinki, Finland, Wahlbeck, Forsén, Osmond, Barker, and Eriksson (2001) reported on the relationship between factors indicative of prenatal undernutrition and the later development of Schizophrenia. This study found that children born to mothers with a low body mass index (BMI) prior to parturition, who were born with small placentas, and were below-average length and weight at birth, had an increased risk of developing Schizophrenia in adulthood. Furthermore, this study indicated that, independent of other predictors, children thin at 7 years of age had an increased risk for developing Schizophrenia in later life. The data also indicated that children short at birth who remained lean during childhood had a fourfold risk of developing Schizophrenia. The authors observed no differences in the risk for Schizophrenia between groups of varying SES, replicating findings from other studies.

The researchers argued that these results are consistent with the hypothesis that fetal and childhood factors (specifically undernutrition) play a role in the pathogenesis of Schizophrenia. However, given the relatively low and consistent prevalence of Schizophrenia in the population and the relatively high rate of early malnutrition, it may be more plausible to conjecture that early nutritional deficits act as predisposing or triggering circumstances. Regardless, this study suggests that malnutrition statistically increases the risk for later development of Schizophrenia.
Wahlbeck and colleagues (2001) suggest that, in their sample, nutritional status (based on maternal BMI, birth length, and slenderness in childhood) is independent of SES; however, they provide no evidence to bolster this claim. Thus, given the information available, it is impossible to discern if these measures reflect actual undernutrition or are simply corollaries of low SES or a genetic diathesis that increases risk for Schizophrenia.

Taken together, these studies suggest that the prevalence of Schizophrenia and SSPD increases in individuals who are exposed to severe malnutrition early in gestation. The findings of Wahlbeck et al. (2001) also provide evidence that Schizophrenia is (either directly or indirectly) related to suboptimal growth in utero through early childhood.

Hock et al. (1998) speculated about potential mechanisms to explain the findings of their group. First, they noted that it was unlikely that this finding was related solely to nutritional restriction because, if such a correlation existed, one would expect to find significantly higher rates of Schizophrenia and SSPD in developing countries that commonly have serious food shortages. They indicated that it was more likely that the increased prevalence was related to a restriction in a specific micronutrient, stating that these types of deficiencies are frequently observed in both developed and developing areas. This explanation could also account for the apparent independence of SES and nutritional status described by Wahlbeck et al. (2001). This hypothesis could be investigated further by using animal models of specific micronutrient deficiencies occurring at circumscribed times during brain development that reflect a proposed pathophysiology of a disorder, for example, migration defects in Schizophrenia secondary to folate deficiency. This approach could be useful in elucidating the effects of micronutrient deficiencies on neuroanatomy, neurochemistry, and neurophysiology; however, it would fail short in illustrating possible behavioral correlates because there are currently no irrefutable animal models of mental disorders, especially Schizophrenia. Finally, Hoek and colleagues stated, their findings could have resulted from the increased level of birth complications and morbidity associated with early birth found in the most affected famine cohort. However, they noted that areas less affected by the famine experienced similar increases in obstetric complications without the concomitant rise in SSPD, making this potential confound less problematic.

Neugebauer and colleagues (1999) again used the Dutch famine data to investigate possible relationships between prenatal nutritional restriction and the subsequent development of Antisocial Personality Disorder (ASPD). The researchers used diagnostic information regarding ASPD from Dutch military induction records. According to the authors, Dutch psychiatrists considered ASPD to include a constellation of behaviors such as aggression, history of criminal activity, disregard for the truth, impulsivity, volatile temperament, unreliability, and interpersonal difficulties. Furthermore, psychiatrists categorized individuals under the subclassifications of violent or nonviolent ASPD.

Results indicated that individuals exposed to severe malnutrition in utero during the first and/or second trimesters had an increased risk for the emergence of later ASPD (specifically violent ASPD) compared to either unexposed individuals, individuals with only moderate levels of caloric restriction, and individuals severely malnourished in the third trimester alone. Malnutrition remained predictive, even after they included other proven or potential risk factors (such as low social class, low IQ, and large sibship size), for ASPD in multiple regression equations. The authors comment that the most likely explanation for this pattern of results is the lack of a particular unspecified micronutrient during this critical period of brain development. They argue that similarities in infant morbidity between cases and noncases, specificity of time and place of the findings, and the lack of third trimester effects indicate that severe malnutrition (during the first/second trimester) supersedes other environmental insults. However, they also propose a possible mechanism in which malnutrition potentiates preexisting genetic or environmental vulnerabilities.

Using a cohort of low birthweight (LBW) children, Breslau, Chilcoat, Johnson, Andreski, and Lucia (2000) examined the relationship between LBW, soft neurological signs, and subsequent intellectual/behavioral functioning at ages 6 and 11. Soft neurological signs refer to a number of various subtle neurological abnormalities in sensory, motor, and integrative skills that do not significantly impact an individual's overall functioning but may still result in suboptimal abilities in these domains (Breslau et al., 2000). Of particular importance, soft signs are not thought to reflect focal brain damage but rather a diffuse neurological pathology resulting from a variety of sources, including genetic anomalies such as microdeletions or mosaics (Breslau et al., 2000). Furthermore, studies have linked soft neurological signs to early malnutrition and deficits in IQ and behavioral functioning (Breslau et al., 2000; Galler, Ramsey, Solimano, Kucharski, & Harrison, 1984).

Breslau et al. (2000) observed a relationship between LBW and the occurrence of soft neurological signs in which LBW children are nearly twice as likely to exhibit soft signs as normal birthweight (NBW) children. The researchers found a linear relationship between LBW and the frequency of soft signs. Thus, the lower a child's weight at
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birth, the more likely he or she would display soft signs. Moreover, the data indicated that children evidencing soft signs consistently performed below average on tests of intellectual abilities regardless of birthweight; however, LBW children tended to score lower on the IQ test in general, thus indicating additive influences. They also found a relationship between soft signs in both LBW and NBW children and the occurrence of learning disorders (at age 11) and the occurrence of internalizing problems at age 6 and 11. In the LBW group, the investigators found a relationship between soft signs and the occurrence of externalizing behaviors, including attention problems, at age 6 but not at age 11.

Even though this study did not strictly deal with nutritional deficits, it is interesting because LBW and soft signs may be associated with undernutrition. This is particularly germane to the Breslau et al. (2000) study because many of the participants, especially those in the LBW group, lived in urban settings and came from low SES backgrounds and thus had an elevated risk for prenatal and/or postnatal malnutrition. Regardless of the nexus between LBW and soft neurological signs, the findings suggest that LBW children may be at increased risk for reductions in IQ, learning disabilities, internalizing problems, and, when younger, externalizing difficulties, including attention deficits. The reason for the apparent evaporation of differences in the externalizing domain may be increased levels of externalizing behaviors exhibited by the control groups (Moffitt, 1993) or the beneficial effects of behavioral/medical interventions.

In a follow-up to their 1986 study (to be discussed in a subsequent section of this chapter), Galler and Ramsey (1989) assessed a group of previously malnourished Barbadian children for symptoms of hyperactivity. Using parent and teacher reports, they found increased levels of hyperactivity and distractibility. These relationships remained consistent after taking into account environmental factors such as parental involvement, parental career/knowledge of the world, stability of the home environment, number of siblings, and quality of living conditions (e.g., quantity of modern conveniences and durability of dwelling construction). Furthermore, these results concur with earlier findings (Galler, Ramsey, Solimano, & Lowell, 1983), which suggested increased attention difficulties in previously malnourished children between 5 and 11 years of age. The current study revealed an increased prevalence of speech difficulties in the formerly malnourished children as noted by teacher report. However, difficulties with socialization, emotional reactivity, and immaturity previously observed in these children (Galler, Ramsey, Solimano, & Lowell, 1983) were not seen in the current investigation. According to the authors, this may have resulted from slight changes in the assessment tools (necessary to reflect the older age of the children) or interventions targeted at ameliorating some of the effects of early malnutrition. If the latter is the case, it is meaningful because it suggests that some aspects of early malnutrition (e.g., social skills) may be more amenable to educational interventions than others (e.g., attention problems; Galler & Ramsey, 1989). However, it is possible that effects such as emotional instability are more characteristic of younger children who were previously malnourished and would disappear in older children regardless of interventions (Galler & Ramsey, 1989). A shortcoming of this study is the researchers' failure to control for intellectual abilities. Thus, it is unknown if the increased attention problems observed in the experimental group are a unique aspect of undernutrition in the 1st year of life, or are a corollary of the lower intellectual skills previously reported in these children (Galler, Ramsey, & Forde, 1986).

Although not as robust as the findings for Schizophrenia, these studies imply that pre- as well as postnatal malnutrition predisposes individuals for exhibiting a variety of externalizing behaviors. It is intriguing to speculate whether the brain is susceptible to insults causing externalizing behaviors for a longer period during development, or if there are distinct etiologies of externalizing disorders, potentially linked to disruptions at various stages of brain development. Nevertheless, this handful of studies provides an impetus for future investigations on the role of malnutrition and other neurobiological risk factors in the etiology of externalizing problems.

A. S. Brown and colleagues (1995) investigated the relationship between prenatal famine exposure and the later development of affective disorders (affective psychosis and neurotic depression). The researchers defined affective psychosis and neurotic depression in accordance with ICD-9 definitions. Thus, individuals with affective psychosis displayed disturbances in mood (either depression or mania) accompanied by mood-congruent delusions, whereas individuals with a diagnosis of neurotic depression displayed disturbances in mood (including symptoms of depression and/or anxiety) but evidenced no psychotic symptoms. They formed the groups by matching birth date and location with psychiatric admission records from 1978 to 1991.

Prenatal exposure to famine in the second trimester increased the risk of developing affective psychosis in later life; however, the authors did not find increased risk of affective psychosis resulting from first or third trimester famine exposure. These results remained significant when
sex was taken into account; however, there was a significant interaction between sex and second semester famine exposure: Males but not females appeared to be at greater risk for developing affective psychosis after second semester famine exposure, whereas females had higher prevalence rates in general. The data indicated no increased risk of neurotic depression following prenatal famine exposure in any trimester or in either sex.

A possible reason for the disparity between the diagnostic categories may be that, when compared to neurotic depression, affective psychosis represents a more severe mood disorder with a greater risk of hospitalization. Furthermore, neurotic depression may be more likely triggered by life stressors, and thus differences between groups could be submerged by random variation in the population. A limitation of this study is that females usually begin exhibiting mood symptoms in adolescence. Therefore, effects of prenatal famine exposure may be observed in females if the researchers reviewed earlier hospital admission records. Additionally, A. S. Brown and his collaborators (1995) caution, their findings may represent the increased prevalence of affective psychosis, but instead may reflect an increased need for hospital admission or delayed onset of symptoms in prenatally famine-exposed males. Nevertheless, these results suggest that males are at greater risk for developing serious mood disorders following significant midgestational malnutrition.

In a follow-up to their 1995 study, A. S. Brown and colleagues (2000) greatly increased their sample size by obtaining new diagnostic records. The researchers focused on unipolar and bipolar depression requiring hospitalization. Exposure to famine during the second and third trimesters related to increased hospital admissions in both males and females with unipolar and bipolar depression. The authors indicated that this effect was particularly robust if exposure occurred in the third trimester only. These results extend the findings of the 1995 study and suggest that prenatal famine exposure predisposes adults to develop serious mood disorders requiring hospitalization and characterized by either depression or mania/hypomania.

Thompson and his collaborators (Thompson, Syddall, Rodin, Osmond, & Barker, 2001) examined the relationship between LBW and the incidence of depression in old age. These investigators used data obtained from individuals born between 1920 and 1930 in the English county of Hertfordshire and who still lived in the area in the early 1990s. The authors assessed all of the participants for depressive symptoms using two measures (a self-report questionnaire and a semistructured interview) and simultaneously asked about confounding factors such as SES, recent loss, general illness, and coronary heart disease (CHD).

This study found a relationship between birthweight and depression in late life: The lower a child's birthweight, the greater the risk for developing late-life depression. The findings were more robust in males and remained significant when the researchers statistically controlled for other complicating factors such as illness, SES, and bereavement. When they specifically took into account the occurrence of CHD (another risk factor for late-life depression), the relationship grew stronger. The research indicated that males with LBW but high weight at 1 year exhibited the highest risk for late-life depression; conversely, males with above average birthweight and comparatively low weight at 1 year exhibited the lowest risk for late-life depression. Thompson et al. (2001) conjectured that this pattern indicated poor prenatal nutrition followed by compensatory growth and good prenatal nutrition followed by a regression to the mean, respectively. Because this study focused on current and not early life depression, the results should not be generalized to depression occurring outside of old age. The authors suggested that their findings provide support for aberrant fetal programming (see the conclusion of this chapter) caused by undernutrition as the major factor contributing to the future development of depression.

In summary, prenatal malnutrition appears to increase the risk for developing internalizing disorders (specifically mood disorders). It is interesting that the risk period for exposure to malnutrition in the externalizing and internalizing domains may be later than for the Schizophrenia Spectrum Disorders. The stages of brain development affected during these periods of vulnerability concur with research on the neurological sequelae of these various psychopathologies and support the timing of onset and duration of insult hypothesis. For example, the research on Schizophrenia strongly suggests that malnutrition exerts its effects in early stages of central nervous system (CNS) development, neural tube formation, and initial neuronal migration, all of which have been implicated in the etiology of Schizophrenia (Arnold, 1999; LaMantia, 1999; Rioux, Nisanov, Lauber, Bilker, & Arnold, 2003; Susser, Brown, et al., 1998). The later period of vulnerability observed in externalizing and internalizing disorders suggests that malnutrition disrupts later processes of brain development such as neurotransmitter formation, late-stage migration, and gliogenesis. Abnormalities in these processes have been implicated in the etiology of externalizing and internalizing disorders (Bowley et al., 2002; Cotter, Pariante, & Everall, 2001; Jenike et al., 1996). Further, some conditions (such as Schizophrenia) may be associated with a relatively acute
injury, whereas behavioral disturbances in the externalizing and internalizing domains may be associated with insults extending over longer periods.

Despite the paucity of studies on this topic, the investigations undertaken with the Dutch famine cohort and similar samples suggest that early malnutrition increases the risk for the later development of mental disorders. Furthermore, this effect is not a general increase in vulnerability, but appears to depend on the timing and duration of the nutritional insult. Because the Dutch famine studies lack confounds such as social class, deprived environment, parental education, and extended postnatal malnutrition (which frequently accompany early malnutrition), they cannot be generalized to a chronically malnourished population. However, they provide strong support for the unique contribution of severe prenatal malnutrition in the emergence of later psychopathology.

Regrettably, few studies have addressed the role of postnatal or pre/postnatal malnutrition in the development of psychopathology. This is particularly disheartening because postnatal malnutrition is common throughout the world, and, as discussed later in the studies on cognition, it is likely that postnatal malnutrition is associated with deficits that differ from those of prenatal malnutrition.

The previous discussion suggests that early malnutrition may lead to the later development of psychopathology. Moreover, the expression of a particular psychopathology likely depends on when the insult occurred (e.g., prenatal versus postnatal or first versus second/third trimester). Another contributing factor (discussed in greater detail in the concluding remarks) is that malnutrition may exert its maximal effect if it occurs concurrently with another insult such as stress or toxicity.

Now that a plausible link has been established, it is necessary to take a step back to examine what may underlie the development of these conditions. We first examine human studies that have been designed to determine if early malnutrition results in adverse effects on cognitive/intellectual development.

PRIMER

Before beginning this section, it is necessary to note that human protein energy malnutrition or undernutrition rarely exists without concomitant micronutrient deficiencies (Gorman, 1995; Kretchmer et al., 1996).

Human Studies of Cognitive Development

One of the shortcomings of research on humans is the difficulty controlling for all potentially relevant variables, sometimes even known confounds. This limitation is particularly vexing in epidemiological research regarding the long-term consequences of early malnutrition. For example, as previously discussed, early malnutrition rarely occurs independently of other risk factors such as poverty (Engle et al., 1996; Pollitt, 1969; Stein & Susser, 1985; Tanner & Finn-Stevenson, 2002). Although there are statistical techniques that can help compensate for this comorbidity, one must still be careful when making inferences regarding experimental interventions or the interplay of particular risk factors. Secondarily, many studies using a population-based design are unable to account for other known or conjectured risk factors such as genetic predisposition, parental education, maternal stress, chaotic home environment, or other complicating physical factors such as toxin exposure, infection, or birth complications (Grantham-McGregor, 2002; Pollitt, 1969). These caveats are not indictments of these types of studies, because what such studies lack in elegant controls they often make up for in direct relevance. However, the limited control over potential third variables should be kept in mind when evaluating such studies.

There are numerous studies detailing the effects of early malnutrition on human cognitive development (Georgieff & Rao, 2001; Gorman, 1995; Pollitt, 1988). Many of these studies were conducted in developing countries, where malnutrition (or, perhaps more frequently, undernutrition) is likely chronic and may span all of development—from the periconceptional phase to adolescence and young adulthood (Grantham-McGregor, 2002). Given the growing minority and immigrant populations of developed countries such as the United States and the fact that a vast portion of children worldwide suffer from early malnutrition, a careful consideration of these studies is warranted, even for those primarily interested in industrialized populations (Pollitt, 1994). Furthermore, knowledge of successful nutritional interventions in developing countries may help to improve current U.S. government programs such as the Women, Infants and Children (WIC) program (Pollitt, 1994; Tanner & Finn-Stevenson, 2002). It is useful to review this literature to provide insight into the broad behavioral effects of early malnutrition. Further, research has linked intellectual/cognitive deficits to various types of psychopathologies (Moffitt & Caspi, 2001). Although this link may not be causal, these conditions (i.e., cognitive abilities and psychopathology) may nonetheless be connected.

Studies on neurocognitive outcomes of children who suffered early malnutrition is presented in three sections: studies concerning prenatal malnutrition and effects of LBW (where the fetus is protected from certain environmental factors such as poverty), studies on postnatal or
combined pre- and postnatal malnutrition, and studies examining the effects of nutritional interventions with malnourished populations.

LBW children or children born small for gestational age (SGA) are usually the result of intrauterine growth retardation (IUGR), which is frequently associated with fetal PEM (Georgieff & Rao, 2001). Although nutritional deficits in SGA babies can result from poor maternal nutrition, they can also result from other gestational or fetal problems such as maternal hypertension, uterine infections, or genetic disorders (Georgieff & Rao, 2001).

Numerous studies have examined the neurocognitive functioning of SGA children (Georgieff, Hoffman, Pereira, Bernbaum, & Hoffman-Williamson, 1985; Low et al., 1982; Pollitt, 1996; Stein et al., 1972). Strauss and Dietz (1998), using data from the National Collaborative Perinatal Project, compared the intellectual performance and visual-motor skills of IUGR children with that of their same sex non-IUGR siblings and NBW children (without IUGR siblings). These researchers demonstrated that IUGR infants are usually born to shorter women who weigh less than the average female. Furthermore, this study revealed that NBW siblings of IUGR children were typically smaller than other NBW children, although they were not considered SGA. The authors found that, at 7 years of age, formerly IUGR infants with a head circumference significantly below normal or less than their siblings' evidenced reduced intellectual capacity and visual-motor skills compared to NBW children. However, the performance of IUGR children did not significantly differ from their non-IUGR siblings, although the data trended in this direction.

These findings suggest that reduced birthweight is a phenomenon considerably influenced by genetic factors, although it is possible that the NBW siblings were malnourished, albeit at a lesser level than their SGA siblings. Additionally, statistically correcting for genetic and environmental agents suggests that IUGR alone does not substantially contribute to the reductions in cognitive abilities noted in other studies. However, these data indicate that IUGR infants born with significantly decreased head circumference differ from the NBW population, other IUGR children without reduced head circumference, and their siblings in terms of their intellectual and visual-motor skills at 7 years of age.

In contradistinction to this study, Low and colleagues (1982) failed to find a relationship between IUGR and cognitive deficits. Their results indicated that IUGR children remained smaller than their peers at 6 years of age; however, the data revealed no significant long-term effects of IUGR on cognitive, motor, sensory, or language abilities. The IUGR group exhibited higher rates of certain difficulties (such as increased language difficulties and a slightly higher fail rate in senior kindergarten), but these differences did not reach statistical significance.

The authors admitted that the small IUGR male sample may have limited statistical power to detect delays in language skills, and they rightly point out that all of the children in this study were full term, preventing generalization to preterm IUGR infants. Furthermore, this study did not assess specific neurocognitive functions (e.g., attention and recognition memory) that, because of their mediation by the hippocampus, might be more susceptible to prenatal insults such as IUGR. It is also possible that intervening environmental factors (such as a quality home environment) attenuated deficits in IUGR children. Another explanation rests on the fact that the authors meticulously matched the IUGR and control groups on factors such as obstetric complications, newborn characteristics, socioeconomic variables, and status at 1-year follow-up; thus, factors potentially contributing to the reduced cognitive performance of IUGR children in previous studies might have been eliminated in the present investigation. Moreover, although not expressly stated in this paper, it is probable that the children in both IUGR and control groups received adequate postnatal nutrition.

Other studies have expressly examined the effects of decreased head growth and caloric restriction on cognitive skills (Georgieff et al., 1985; Harvey, Prince, Bunting, Parkinson, & Campbell, 1982). Winick and Rosso (1969) demonstrated that children dying of severe malnutrition in the 1st year after birth evidence reduced brain DNA content, indicative of fewer neuronal and glial cells. Reduced head growth secondary to reduced cell numbers is an important variable to consider because microcephaly (severely reduced head size) is linked to neurodevelopmental disorders such as Fetal Alcohol Syndrome. Furthermore, some investigators have correlated small head circumference at birth with greater risk for developing psychiatric disorders such as Schizophrenia (Archibald et al., 2001; Bracha et al., 1995; Kunugi, Takei, Murray, Saito, & Nanko, 1996). Although reduced head growth is not associated with development in a specific brain region, it may be an indirect indicator of general brain maturation (Pollitt, Mueller, & Leibel, 1982).

Georgieff et al. (1985) showed that SGA infants and infants who were a size appropriate for gestational age experiencing a prolonged period of postnatal caloric deprivation (due to medical complications) exhibited reduced rates of catch-up head growth. As would be expected, SGA infants began showing this reduced growth rate after sustaining a shorter period of caloric deprivation. The reduced rates of catch-up growth in these infants
resulted in smaller head circumference at 1 year, head growth curves that (although broadly within the normal range) continued to be less than optimal, and, in the most severely affected infants, below average motor development scores.

Harvey and colleagues (1982) found that children born SGA with intrauterine head growth that slowed prior to 26 weeks gestation obtained lower scores on tests of perceptual and motor skills at 5 years of age. SGA children with normal head growth performed at the same level as controls in these and other cognitive domains. The researchers combined the two SGA groups and evaluated performance strictly in terms of birthweight, ignoring rate of head growth; they determined that (taken as a single group) SGA children did not perform significantly differently from controls. Although this study did not deal with frank undernutrition, these results are an interesting corollary to the findings of Georgieff et al. (1985) because they indicate that early rate of head growth may have a long-term impact on certain cognitive abilities.

Although not entirely consistent, these studies suggest that SGA infants, especially those with decelerated rates of head growth, and children who have lower birthweight compared to siblings are at higher risk for developing subtle but detectable neurocognitive difficulties (Georgieff et al., 1985; Harvey et al., 1982). In addition, Tirosch, Gaster, Berger, Cohen, and Scher (2000) showed that birthweight and head circumference of typically developing children positively and significantly correlated with activity level and mobility in infancy. However, prenatal malnutrition in the absence of other risk factors has not been convincingly demonstrated to result in long-term decreases in cognitive abilities. It remains unclear how meaningful any deficits will be as previously malnourished children age (Guesry, 1998; Pollitt, 1996; Stein et al., 1972; Stein & Susser, 1985). Nevertheless, the relationship noted by Tirosch et al. is important because it suggests that babies born with low birthweight are less active and less able to explore their environment, thereby potentially reducing mental stimulation, which human and animal studies indicate is necessary for basic cortical organization and development (Black, 1998; Nelson, 1999). Researchers theorize that environmental stimulation is also critical for the development of other, more complex cognitive skills (Black, 1998; Nelson, 1999, 2000).

It is necessary to qualify these assertions. First, it is quite likely that the SGA infant is affected by the internal and external environments into which she or he is born, for example, by such factors as maternal substance use, stress, and genetic constitutions; postnatal nutritional factors; and birth complications such as premature birth, hypoxia, and maternal infections. Therefore, the ultimate effects of SGA are likely graded on a continuum, depending on the combination of other vulnerabilities and assets possessed by the child (Engle et al., 1996; Stein & Susser, 1985).

Second, as stated previously, SGA infants are a heterogeneous group, and it is plausible that different etiologies of IUGR have different effects on neurological development (Black, deRegnier, Long, Georgieff, & Nelson, 2004). Finally, evidence suggests that prenatal malnutrition (especially if endured early in pregnancy) can occur without resultant low birthweight (Heasman, Clarke, Stephenson, & Symonds, 1999; Lumey, 1998). Lumey determined that prenatal malnutrition restricted to the first trimester resulted in compensatory placental growth without subsequent reductions in birthweight. For this reason, normal birthweight does not necessarily indicate the presence of adequate prenatal nutrition.

Thus, many children, despite being born the appropriate size for gestational age, may have sustained neurological insults due to prenatal malnutrition. These children, as well as SGA children, may be more vulnerable to further nutritional deprivation or other environmental insults (Berkman, Lescano, Gilman, Lopez, & Black, 2002; Galler et al., 1986; Galler & Ramsey, 1987, 1989; Ivanovic et al., 2000, 2002; Liu, Raine, Venables, Dalais, & Mednick, 2003). It is therefore difficult to dissociate the precise effects of prenatal malnutrition because the populations typically studied may not represent all prenatally malnourished individuals.

In a series of papers, Galler and colleagues (Galler & Ramsey, 1987, 1989; Galler, Ramsey, Soliman, & Lowell, 1983; Galler, Ramsey, Soliman, Lowell, & Mason, 1983; Galler et al., 1986) described the consequences of moderate to severe malnutrition sustained by Barbadian children in the 1st year of life. Galler et al. (1986) showed that, despite apparently successful nutritional rehabilitation, previously malnourished children continued to exhibit lower performance on tests of intellectual abilities up to 8 to 14 years postmalnutrition. In this study, researchers administered to participants the Wechsler Intelligence Scale for Children-Revised (WISC-R; Galler et al., 1986), and the participants' mothers completed a questionnaire assessing living circumstances, education, family relationships, and caregiver contact, among other factors. Consistent with previous evaluations (Galler, Ramsey, Soliman, Lowell, et al., 1983), results indicated that previously undernourished children had lower overall intellectual abilities and performed below controls (matched on birthweight, medical illnesses other than malnutrition, age, sex, and handedness) on the verbal and performance subscales of the
WISC-R. The researchers observed no sex differences or sex-nutrition interactions, except that (regardless of early nutritional status) females outperformed males on the Freedom from Distractibility Index.

Galler et al. (1986) reported a significant correlation between scores on the WISC-R and environmental factors (e.g., poverty and maternal employment). However, early malnutrition remained significant when the authors statistically adjusted for these influences. Conversely, environmental factors remained significant when the authors statistically adjusted for early nutritional status. The significant influence of environmental factors on test performance at these older ages is interesting because this was not found in previous investigations with this cohort (Galler, Ramsey, Solimano, Lowell, et al., 1983). The authors concluded that a history of malnutrition continues to play a role in intellectual deficits at least into adolescence. However, as a child matures, the effects of an early nutritional insult may be overcome or attenuated by other environmental factors. Thus, the findings suggest that appropriate interventions may be effective in combating some of the intellectual impairments incurred in early malnutrition.

Using this same cohort, Galler and Ramsey (1987) found that previously malnourished children younger than 14 displayed deficient performance on Piaget’s tests of conservation. These differences were not entirely accounted for by IQ, suggesting that these tasks assess slightly different cognitive domains. In contrast to the persisting differences on measures of IQ, previously malnourished children performed equivalent to controls by age 14. This pattern is similar to that observed in the Galler et al. (1986) study in that it suggests that effects of an early nutritional insult, initially very salient, grow less robust with time.

Another series of papers by Ivanovic and collaborators (Ivanovic et al., 2000, 2002) investigated the effects of severe early malnutrition on scholastic achievement, IQ, and brain morphology in Chilean high school graduates. Formerly undernourished and never undernourished high school graduates of low SES participated in this study. Researchers found that individuals with a history of early malnutrition obtained lower Full-Scale IQs (as assessed by the Wechsler Adult Intelligence Scale [WAIS]), lower scores on a scholastic aptitude test containing verbal and numerical items, and reduced brain volume on magnetic resonance imaging (MRI). The IQ results remained consistent across verbal and nonverbal domains in both sexes, whereas the brain volumetric difference, though significant in both sexes, emerged much more strikingly in males.

In a subsequent study with a similar population, Ivanovic et al. (2002) evaluated two groups of young adults with mean IQs of about 125 and 91, respectively. Both groups included individuals of high and low SES. They assessed participants with the same battery as in the 2000 study, now adding intellectual testing of both parents. The researchers verified the occurrence of malnutrition in the 1st year of life by reviewing hospital records. The results indicated that, regardless of SES, children with higher IQ had greater brain volume, higher maternal IQ, better prenatal nutrition as indexed by birthweight, no evidence of postnatal nutritional deficits, and higher scholastic achievement. Maternal IQ, brain volume, and postnatal nutrition significantly related to young adult IQ. Early malnutrition rarely occurred in the high SES, low IQ group; however, this group evidenced lower maternal IQ when compared to the high SES, high IQ group. Conversely, 64% of individuals with low SES and low IQ had a history of early malnutrition, and this group, in general, had maternal IQs lower than the other three groups. Additionally, the individuals in the low IQ group had similar maternal IQ, scholastic achievement, and brain volume. This led the authors to conjecture that these findings are typical correlates of low IQ.

Liu et al. (2003) conducted a very interesting study in which they assessed the effect of malnutrition at age 3 on cognitive skills at age 3 and again at age 11, while attempting to statistically control for various psychosocial risk factors (e.g., living circumstances, parental education, age of mother at time of birth, presence of mental illness in the mother, and number of children living in the home). Study participants included children living on the island of Mauritius and enrolled in the Mauritius Child Health Project, a prospective longitudinal study of children’s physical and psychological health. At 3 years, children were assessed for several indicators of malnutrition: angular stomatitis, kwashiorkor, sparse fine hair, and anemia. These indicators are associated with deficiencies in vitamin A and B₁₂; protein, zinc, and copper; protein energy, zinc, and iron; and iron, respectively. The researchers considered a child malnourished if he or she displayed one or more of these four indicators. Assessments at age 3 included subtests from the Boehm Test of Basic Concepts-Preschool Version. Assessments at age 11 included subtests from the WISC, Trails A & B (tests of executive functions), and a test of basic reading skills.

Results indicated that children malnourished at 3 years displayed overall intellectual and verbal cognitive deficits and continued exhibiting these deficits at age 11. Moreover, at age 11 these children exhibited deficits in nonverbal abilities, scholastic skills, reading abilities, and executive functioning. They found that even though
malnourished children tended to have lower parental education and higher scores on measures of social stress, the effects of malnutrition remained significant when these factors were statistically adjusted for in the analysis. Additionally, this study reported a dose-response (i.e., monotonic) relationship between indicators of malnutrition and cognitive skills, as assessed by the WISC. Thus, children with three of four indicators of malnutrition at age 3 had an IQs approximately 15 points below the mean, children with two indicators had an IQ 9 points below the mean, and children with one indicator had an IQ only 3 points below the mean.

The authors reported that anemia at age 3 years was the most significant indicator relating to lower cognitive performance at ages 3 and 11. The researchers acknowledged that they did not obtain nutritional information at age 11; hence, it is possible that these results could be explained by current or chronic malnutrition. Furthermore, the authors did not examine birth records. Therefore, factors such as birthweight and prenatal complications may have influenced the results. Nonetheless, this is a strong experimental design supporting the hypothesis that postnatal malnutrition has repercussions for later cognitive functioning. It also suggests that trace nutrients such as iron are particularly important in the manifestations of malnutrition.

The unique impact of postnatal malnutrition and its relationship with other risk factors on cognitive development remains unknown. In general, the studies presented here suggest that postnatal malnutrition is associated with discernable decreases in intellectual abilities (Berkman et al., 2002; Galler et al., 1986; Galler & Ramsey, 1987; Liu et al., 2003). Even though this assertion appears supported by the extant data, caution similar to those detailed in the section regarding prenatal malnutrition still apply. For example, many of these studies did not directly assess potential confounding factors commonly associated with early malnutrition, such as parental IQ, biological risks (birth complications, childhood diseases, or environmental toxins), and social variables (such as a chronically neglectful or understimulating environment; Berkman et al., 2002; Guesry, 1998; Liu et al., 2003; Pollitt, 1969; Stein & Susser, 1985). Nevertheless, a majority of the studies indirectly assessed important variables and controlled for these variables in their subsequent analyses (Berkman et al., 2002; Galler et al., 1986; Galler & Ramsey, 1987; Liu et al., 2003), allowing us to be fairly confident in the assertion that postnatal malnutrition exerts deleterious effects on the developing brain.

The studies reviewed above continue to leave open the question of amelioration of the effects of early malnutri-

tion on the developing brain. Several studies addressing this point are considered next.

Generally, studies that examine amelioration of early malnutrition investigate either strictly nutritional or combined environmental/nutritional interventions (Joos, Pollitt, Mueller, & Albright, 1983; Lien, Meyer, & Winick, 1977; Pollitt, 1996; Raine, Mellingen, Liu, Venables, & Mednick, 2003; Raine et al., 2001; Winick, Meyer, & Harris, 1975; Zeskind & Ramey, 1981). The individuals in these studies are usually assumed to suffer from postnatal malnutrition, although many of the investigations did not explicitly rule out the possibility of prenatal nutritional restriction.

Pollitt and his collaborators (Pollitt, Gorman, Engle, Martorell, & Rivera, 1993) described a nutritional intervention in four rural Guatemalan villages. Beginning at various times during development (e.g., before conception, during gestation, throughout lactation, and into childhood), this project provided pregnant mothers and their children with either a high-protein, high-calorie drink known as Atole or a low-protein, low-calorie drink known as Fresco. The researchers fortified both beverages with trace minerals. Individuals in two villages received the Atole drink and individuals in the others received Fresco. Children of low SES whose mothers received Atole during gestation and until at least age 2 outperformed their peers on tests of information processing, mental ability, and academic skills, and progressed further in school than children receiving Fresco. Low SES children with shorter and later (beginning at or after age 2) periods of exposure to Atole also benefited (scoring higher on tests of numerical and reading abilities and progressing further in school than their peers), although these findings were less striking. These results are interesting because they argue for a stable, long-term improvement in intellectual, academic, and cognitive skills resulting from prenatal through postnatal nutritional supplementation in undernourished populations. Moreover, they imply that supplementation has the greatest impact/benefit on low SES individuals, perhaps because it delivers help to the children who, without it, would have fared worst. They also illustrate the differential vulnerability (or plasticity) of the brain depending on the timing of the insult and intervention.

Using data from the Mauritius health project, Raine et al. (2001) investigated the effects of an enriched educational environment on orienting and physiological arousal (measured by electroencephalography). In this study, experimenters matched children based on psychophysiological characteristics at age 3 and randomly assigned participants to an enriched preschool or a standard pre-
school educational experience on the island of Mauritius. The enriched preschool employed various types of enriching experiences, including well-balanced meals, education about nutrition and hygiene to parents and children, encouragement of imaginative play, interactive conversational skills, socialization, exercise, and regular field trips. Furthermore, parental involvement was highly encouraged, time-out discipline was used instead of corporal punishment, and the children's health was carefully monitored. The enriched experiences lasted for 2 years, at which time the children began grade school in typical classrooms.

Results indicated that the enriched preschool experience related to increases in orienting and physiological arousal at age 11. The authors speculated that these findings provided evidence of improved information processing or accelerated neurological maturation in children enrolled in the enriched preschool. They acknowledged that, given the multifactorial nature of the enriched experience, it was impossible to surmise which component or components explained these results, although research suggests that both nutritional and educational enrichment have unique effects on cognitive development (Grantham-McGregor, Powell, Walker, & Himes, 1991). However, these results may be explained by long-term changes in parental or child behavior caused by the early preschool experience. For example, the parental education and increased parental involvement encouraged by the preschool may have been built on and maintained after the child began grade school. Thus, the findings may represent the consequence of being raised in a more stable, lower-stress home environment and not by neurological alterations directly induced by the preschool experience. Regardless, these findings suggest that long-term alterations in physiological parameters, considered to reflect neuronal processing (Williams et al., 2000), can occur secondary to environmental enrichment and nutritional supplementation. These results are fascinating because reduced orienting and arousal responses are associated with various types of psychopathology (Banaschewski et al., 2003; Perry, Felger, & Braff, 1998; Schnur et al., 1999).

The previous studies illustrate the potential benefits of nutritional supplementation and combined nutritional/environmental enrichment in chronically undernourished populations. However, as discussed previously, undernourished children are frequently born with other genetic and environmental risks (Guesry, 1998; Pollitt, 1969; Stein & Susser, 1985). This begs the question: Can comprehensive environmental enrichment rescue a child with multiple risk factors, including malnutrition?

Winick et al. (1975) and Lien et al. (1977) addressed this question by investigating the intellectual performance of Korean children who suffered early malnutrition (prior to the age of 2) but were subsequently adopted into homes in the United States. Winick and colleagues showed that even the most severely malnourished children (below the 3rd percentile for height and weight at or before age 2) made significant advances in their physical and intellectual development after adoption. Specifically, in middle childhood, the previously malnourished children attained heights and weights above the standard for Korean children (although they continued to be smaller than American children). Furthermore, these children achieved IQ scores within the average range (mean of 102) and demonstrated academic performance comparable to their American peers. The researchers suggested that these scores were substantially greater (in excess of 40 points) than would be expected if these children remained in restricted environments. Of particular importance, this study showed a significant difference between the IQs of previously malnourished adopted children and those of adopted children with no history of malnutrition (mean IQ of the latter group was approximately 112). Winick and colleagues conjectured that these differences were partially genetic (the parents of undernourished children being more likely to have lower intellectual abilities), or a consequence of the nutritional deficits (i.e., the previously malnourished children had not been able to benefit as much from the adopted environment). Unfortunately, it is difficult to disentangle these possibilities without an assessment of parental IQ or a sibling design in which the other sibling was not malnourished.

In a study using a similar design, Lien et al. (1977) examined the roles of malnutrition on the cognitive development, growth, and academic achievement of Korean children adopted later in childhood (between 2 and 5 years of age). The researchers again found that severely, moderately, and nonmalnourished adopted children attained weight and height above standards for Korean children but below those of American children. However, they found that severely malnourished children attained IQ scores significantly lower than American children and their nonmalnourished adopted peers. Results also indicated that severely malnourished late adoptees had academic achievement scores below that of their American classmates and their late-adopted peers. The effect of nutritional deficits on academic performance remained significant when age of adoption and age of placement with the adoption agency were taken into account (this analysis was not completed on the IQ information because of the relatively small number of cases with this information provided). Interestingly, the
authors found a significant effect for age of adoption on academic performance, but no evidence relating academic performance to duration of malnutrition or for an interaction between any of these factors. Secondary factors (such as behavioral or emotional concerns) may explain both later age of adoption and below-average performance on IQ and academic tests, but more would have to be known about a child’s preadoptive history to completely discount this confound.

These two studies provide evidence for improved cognitive and scholastic performance following severe malnutrition in adopted children removed from pathological environments. However, the results of the second study suggest that there is a critical period in which environmental enrichment will be maximally beneficial and after which recovery is either slowed or attenuated.

We have seen that environmental enrichment (of varying degrees and types) is able to ameliorate some of the detrimental effects of malnutrition on cognitive skills; however, a subsequent question asks, Would enrichment contribute to a reduction in psychiatric correlates of malnutrition? This is especially interesting because, based on the discrepant findings of Stein et al. (1972) and Susser et al. (1996) with regard to the effect of prenatal famine exposure on cognitive deficits and Schizophrenia, it appears likely that psychopathological conditions may be more sensitive to diffuse neurological disruptions than cognitive abilities, which themselves appear more sensitive than current measures of neuropsychology.

In a follow-up to their 2001 study, Raine et al. (2003) address this question. This study reported that children who experienced the enriched preschool environment exhibited significantly fewer conduct problems and schizotypal personality traits at age 17 and reduced self-reported levels of criminal offending at age 23. Court records of criminal offenses trended toward fewer offenses in the enriched group, but this did not reach conventional levels of statistical significance. Furthermore, the data showed significant interactions between environmental enrichment and early nutritional status. Thus, individuals with poorer nutritional status assessed at 3 years of age (see Liu et al., 2003), prior to the enriched preschool intervention, demonstrated significant benefits from the program. Specifically, in addition to the results presented here, the undernourished group evidenced reduced interpersonal deficits at age 23 when compared to undernourished nonenriched controls. Subsequent analyses to account for psychosocial risk factors (see Liu et al., 2003) and physiological factors at age 3 revealed no moderating effects or changes in the results. The authors argue that their findings indicate long-term behavioral benefits of enriched environmental experiences and a particularly striking long-term improvement in functioning of previously malnourished children. They acknowledge that which aspects of the enriched preschool experience contributed the most to the observed differences cannot be identified. However, they contend that the improved nutrition offered by the preschool likely played a role, especially with regard to the children who had previous nutritional deficits. This hypothesis is consistent with the findings of other research studies indicating a unique effect of nutritional supplementation on cognitive development (Grantham-McGregor et al., 1991).

The studies reviewed here (in addition to many other investigations) suggest that environmental enrichment moderates the effects of malnutrition, albeit through direct supplementation or combined nutritional and educational enrichment. Some questions remain as to how permanent and significant these effects are, but certain data indicate that, if undertaken early in development and for a sufficient duration, the beneficial effects of environmental enrichment can become stable and long-lasting (Lien et al., 1977; Pollitt, 1996; Raine et al., 2001; Winick et al., 1975). However, it would be naïve to assume that all insults, regardless of severity or genetic diathesis, can be completely alleviated by high-quality schools, nutritional supplementation, and supportive parenting (Lien et al., 1977; Pollitt, 1996). No matter the interventions employed, one cannot help but suspect that some conditions remain resistant to complete amelioration. At the same time, the inherent adaptability and plasticity of the nervous system, both in children and adults, attests to the fact that some improvement in many conditions is possible, given proper stimulation (Huntley & Jones, 2002; Nelson, 1999). For example, the studies described by Pollitt suggest that in malnourished, low SES populations, nutritional supplementation alone can have a long-term ameliorative impact on cognitive functioning. Furthermore, the reports by Lien et al., Winick et al., and Zeskind and Ramey (1981) give hope that even individuals with risk factors across multiple domains can profit from quality environmental circumstances. Essentially, plasticity exists; however, recovery from early insults such as malnutrition is likely to be incomplete.

In summary, the studies discussed in this section indicate that early malnutrition has discernable effects on cognitive skills throughout all periods of brain development (gestational and postnatal). However, research also suggests that there is potential for catch-up brain growth and improved intellectual and behavioral development if
nutritional needs are restored. Additionally, other studies suggest that educational and environmental manipulations may also contribute to improved outcomes following early malnutrition. It is possible that some of the manifestations of malnutrition reported in this section (e.g., reductions in intellectual and certain cognitive abilities) may have resulted from impairments secondary to various psychiatric symptoms such as inattention or anxiety. However, with the exception of the Galler and Ramsey (1989) study, these two factors appear not to have been measured concurrently.

At this point, the discussion will again move down another level to focus on findings that shed light on the effects of early malnutrition on the structure and function of the developing and mature brain.

**Neurobiology**

Using a variety of dietary manipulations, many studies have linked early undernutrition to disturbances in neurotransmitter development and function and to neuroanatomic abnormalities, including fine structures (e.g., dendritic spines) and specific regions such as the hippocampus (Almeida, Tonkiss, & Galler, 1996; Hernandez-Rodriguez & Manjarrez-Gutierrez, 2001; Morgane et al., 1993, 2002; Wauben & Wainwright, 1999; Wiggins, Fuller, & Enna, 1984). These are important factors to consider because changes in brain morphology and physiology caused by malnutrition may be similar to the biological alterations observed in various psychopathologies (A. S. Brown et al., 1996).

Neurotransmitters and their receptors are important determinants of brain development before they become a critical part of the information-processing activities of neurons (Benes, Bolte-Taylor, & Cunningham, 2000; Berger-Sweeney, 1998; Bonhoeffer & Yuste, 2002; Fernandez-Ruiz, Berendro, Hernandez, Romero, & Ramos, 1999; Franciosi, 2001; Heine, 1999; Ma et al., 2000; Nguyen et al., 2001; Retz, Kornhuber, & Riederer, 1996; van Kesteren & Spencer, 2003; Whitford, Dijkhuizen, Polleux, & Ghosh, 2002). Thus, if early malnutrition disturbs the balance of neurochemical systems, it could result in structural and/or behavioral alterations (Alvarez et al., 2002; Wauben & Wainwright, 1999; Wiggins et al., 1984).

Disruption of neurotransmitter systems due to early malnutrition can directly or indirectly affect brain development (Wauben & Wainwright, 1999). That is, a neurotransmitter may directly induce a developmental process, for example, GABA in promoting proliferation of neuronal progenitors, acetylcholine’s involvement in apoptosis, serotonin’s role in synaptogenesis, and glutamate’s regulation of dendritic spine formation (Nguyen et al., 2001). Therefore, if early malnutrition greatly reduces or augments neurotransmitter concentration, normal processes may not occur, or may occur in an abnormal fashion (Wauben & Wainwright, 1999). Alternatively, a neurotransmitter may be responsible for modulating other neurotransmitters, growth factors, or signaling molecules (e.g., cytosolic calcium levels, immediate early gene expression, or the mitogen-activated protein kinase cascade), which in turn regulate other developmental processes (Wauben & Wainwright, 1999). All of these downstream events can be disrupted by abnormal neurotransmitter concentrations resulting from malnutrition (Evard, Marret, & Gressens, 1997; Wauben & Wainwright, 1999).

The amino acids tryptophan and tyrosine are precursors of the neurotransmitters serotonin and dopamine, respectively (Benes et al., 2000; Wauben & Wainwright, 1999). The blood-brain barrier contains transporters for these amino acids, which are not directly synthesized in the brain (Wauben & Wainwright, 1999). Therefore, adequate dietary intake is essential to maintain proper CNS concentrations of these compounds. Serotonin is involved in neuronal proliferation and differentiation, glia formation, and synaptogenesis (Gaspar, Cases, & Maroteaux, 2003; Morgane et al., 1993; Okado, Narita, & Narita, 2001; Wauben & Wainwright, 1999).

Hernandez-Rodriguez and Manjarrez-Gutierrez (2001) found increased tryptophan uptake across the blood-brain barrier and serotonin synthesis within the brain of gestationally malnourished rats. They observed these differences through weaning, and the increased serotonin synthesis continued after nutritional rehabilitation and normalization of tryptophan uptake. Based on these animal studies and human research suggesting analogous patterns of plasma-tryptophan ratios, these researchers postulated that similar outcomes are likely in human infants suffering from prenatal malnutrition (see Hernandez-Rodriguez & Manjarrez-Gutierrez, 2001, for review).

Manjarrez, Manuel, Mercado, and Hernandez (2003) conjectured that the increased concentration of serotonin observed in undernourished animals results in a desensitization of the serotonergic system secondary to chronic overactivation. Prenatally malnourished adult and adolescent rats also displayed decreased serotonin uptake sites, decreased serotonin fiber density, and enhanced serotonin release following hippocampal stimulation (Blatt, Chen, Rosene, Vollicer, & Galler, 1994; Chen, Tonkiss, Galler, & Vollicer, 1992; Mokler, Galler, & Morgane, 2003).
In addition, pre- and postnatally malnourished animals exhibit deficits in adaptation of the serotonergic system in response to chronic stress (Almeida et al., 1996; Mokler et al., 2003). Together, these results suggest that prenatal malnutrition can lead to long-lasting or even permanent alterations of the serotonergic system, potentially contributing to the later development of psychopathology (Benes et al., 2000; Fishbein & Pease, 1994; Hernandez-Rodriguez & Manjarrez-Gutierrez, 2001; Manjarrez et al., 2003).

Pre/postnatally undernourished animals also demonstrate reduced reactivity to pharmacological manipulations of the catecholaminergic system (Almeida et al., 1996; Chen, Turiak, Galler, & Volicer, 1997; Soto-Moyano et al., 1999). For example, early malnourished animals showed an attenuated response to dopamine agonists that induced stereotyped motor behaviors, reduced sensitivity to cataleptic symptoms caused by dopamine antagonists, and a developmental delay in the induction of hypoactivity after administration of an adrenergic agonist (clonidine; Almeida et al., 1996; Bredberg & Paalzow, 1990; Goodlett, Valentino, Resnick, & Morgane, 1985). Other studies show decreased concentrations of dopamine and epinephrine receptors in specific brain regions of animals exposed to early undernutrition (Almeida et al., 1996; Wiggins et al., 1984).

Almeida and colleagues (1996) conjecture that these modifications are an adaptive response to initially high levels of catecholamines during brain development in undernourished animals. However, findings of increased sensitivity to the hypothermic effects of apomorphine (a dopamine agonist) but decreased sensitivity to the hypothermic effects of clonidine suggest a more complex picture in which pre/postnatal malnutrition has a differential impact on various subtypes of catecholaminergic receptors and on receptors within certain brain regions (Almeida et al., 1996; Brioni & Orsinger, 1987). For example, using a mild (8%) protein-depleted diet, Soto-Moyano and collaborators (1999) found increased norepinephrine release and neuronal density only in the occipital cortex of prenatally malnourished rats. Again, early malnutrition appears to cause alterations in the catecholaminergic system regardless of the precise dietary manipulation.

Prenatally malnourished animals exhibit reduced sensitivity to the effects of benzodiazepines (BZs; Almeida et al., 1996; Masur & Ribeiro, 1981; Tonkiss et al., 2000; Tonkiss, Trzcińska, Shultz, Vincitore, & Galler, 2000). This class of drugs potentiates the actions of the inhibitory neurotransmitter GABA (Almeida et al., 1996). Researchers observed long-term changes in sensitivity to BZs, similar to those found in the serotonergic system, during malnutrition and following nutritional rehabilitation (Almeida et al., 1996; Tonkiss et al., 2000).

Tonkiss and coworkers (2000) studied spatial learning in prenatally malnourished rats following administration of the GABAergic agonist chlordiazepoxide (CDP) at 30 and 90 days after birth. They found that prenatally malnourished animals responded less than control animals to a high dose of CDP at both 30 and 90 days of age, but at 90 days, the previously malnourished animals displayed greater sensitivity to a lower dose of CDP when compared to well-nourished controls. A possible reason for these differential responses may be that the drug exerts certain effects (e.g., anxiolytic versus amnesic) at high and low doses. The researchers concluded that differences between the GABAergic system of malnourished and well-nourished animals resulted in differential responses to CDP depending on age of administration and particular dosage of the drug.

Researchers have linked early malnutrition to reduced levels of GABA transmitter and increased binding of GABA and BZs to the GABA receptor complex in the CNS of rodents (Almeida et al., 1996). It is probable that the alterations in GABA binding and concentration underlie the attenuated responses to BZs and result from permanent changes in this neurotransmitter system directly caused by early malnutrition (Almeida et al., 1996; Chang, Galler, & Luebke, 2003). Again, changes in this system appear consistent across dietary manipulations, ages, and strains of animals used; therefore, they likely represent actual effects of early malnutrition and are not simply a by-product of a specific experimental design (Almeida et al., 1996). Changes in the developing GABA system are significant because GABA is a very active transmitter in early cortical development (Ben-Ari, 2002; Davies et al., 1998).

Other rodent studies reveal that early malnutrition is associated with lower sensitivity to drugs acting on the opiate system; however, studies showing specific receptor changes have not been completed (Almeida et al., 1996). Similarly, studies indicate reduced cholinergic function in the early malnourished rats (Almeida et al., 1996). Specifically, differences in muscarinic receptor density, binding, and developmental course in different brain regions are seen in previously malnourished rats. However, too few studies have been completed to draw firm conclusions regarding the effect of early malnutrition on the cholinergic system with relevance to possible behavioral effects.

Tonkiss, Almeida, and Galler (1998) used an operant procedure to show that prenatally undernourished female rats displayed sensitivity to the blockade of glutamate receptors with an N-methyl-D-aspartate (NMDA) antagonist (MK-801). The NMDA receptor is a type of glutamate re-
ceptosome highly concentrated in the hippocampus and is thought to play a critical role in learning and memory (Cui et al., 2004; Nakazawa et al., 2003; Roesler et al., 2003). Tonkiss and coworkers trained rats to a stable level of performance on a differential reinforcement of low-rates (DRL) task. On this particular DRL schedule, animals did not receive a reward unless they separated their responses by at least 18 seconds. After attaining a stable performance, the researchers administered MK-801 at various doses. Results indicated that the performance of prenatally malnourished female, but not male, rats was disrupted after MK-801 administration. This experiment is interesting because it is one of the few studies to examine sex differences in generalized prenatal malnutrition. Although speculative, the increased sensitivity to NMDA blockade in prenatally malnourished females may be the result of loss or dysfunction of NMDA receptors in the hippocampus of these animals (J. A. Salinas, personal communication, April, 2000). This explanation is consistent with histological findings in other neurotransmitter systems showing decreased concentrations of various receptor types following nutritional insults (Almeida et al., 1996; Wiggins et al., 1984).

Alternatively, Fiocco and colleagues (Fiocco, Rosene, Galler, & Blatt, 2003) reported that prenatally malnourished rats displayed persistent increases in the concentration of kainate receptors (another type of glutamate receptor) in the CA3 subregion of the hippocampus, a region implicated in recognition memory (Fiocco et al., 2003; Lec & Kesner, 2003). These differences persisted through 220 days of age, but they did not emerge until 30 days after birth. Furthermore, Palmer, Prinz, Butler, Duvall, and Prinz (2004) found evidence of increased NMDA receptor binding in the striatum of prenatally protein-malnourished animals, but they observed no differences in NMDA receptor binding in the hippocampus or dopamine receptor binding in the striatum. These studies suggest that changes in the glutamate system occur in rats secondary to prenatal malnutrition; however, more studies need to be completed to specify the precise nature of these changes across brain regions, age, sex, and subtypes of glutamate receptors.

This research indicates that early malnutrition appears to perturb an animal's responsiveness to pharmacological manipulation of various neurotransmitter systems (Almeida et al., 1996). Many studies show decreased receptor density for several types of neurotransmitters (dopamine, epinephrine, serotonin, acetylcholine, and GABA; Almeida et al., 1996). Researchers postulate that this represents an aspect of homeostatic functioning in early malnutrition in that down-regulation of receptors occurs in response to higher than normal levels of neurotransmitters during development (Almeida et al., 1996; Manjarrez et al., 2003). In addition, malnourished animals show decreased adaptations of the serotonergic and opioid systems in response to stress, possibly indicating permanently altered system dynamics (Almeida et al., 1996; Mokler et al., 2003). Essentially, malnutrition may exert its effects on neurochemistry not solely by affecting a single neurotransmitter system, but by perturbing the intricate balance between systems in the developing brain.

The changes in neurotransmitter systems described here appear to alter how an animal reacts and interacts with its environment. Therefore, if similar biochemical changes occur in the developing human brain, one could speculate that these perturbations will also result in modifications of behavior (Almeida et al., 1996). These behavioral changes may represent interesting correlates of certain forms of psychopathology (Almeida et al., 1996). For example, Almeida et al. (1996) reported on a study finding that, when compared to well-nourished controls, postnatally malnourished animals exhibited an anxiolytic reaction similar to that of Panic Disorder patients after chronic administration of either a tricyclic antidepressant or a monoamine oxidase inhibitor. Furthermore, numerous studies have linked dysfunction of neurotransmitter systems to the expression of various forms of psychopathology (Fishbein & Pease, 1994; Kaufman, Plotsky, Nemeroff, & Charney, 2000; Konradi & Heckers, 2003). In addition to effects on the organization of developing neurotransmitter systems, malnutrition (as noted earlier) affects structures in the brain such as the hippocampal formation. This brain region is particularly susceptible to a wide range of early insults and is implicated in various types of psychopathology (Arango, Kirkpatrick, & Koenig, 2001; De Bellis et al., 2000; Harry & Lefebvre d'Hellencourt, 2003; Heckers et al., 1998; Kimura, Reynolds, & Brien, 2000; Korte, 2001; Laakso et al., 2000, 2001; Walsh & Emerich, 1988).

Morgane et al. (2002) contend that early malnutrition results in decreased serotonergic innervation to the hippocampus due to decreased projections from the median raphe nucleus. However, as noted previously, early malnutrition results in increased serotonin release within the hippocampal formation proper. The authors propose that the disruption in input and local neurotransmitter concentration within the hippocampus leads to increased GABAergic activity in select inner neurons (Chang et al., 2003; Mokler et al., 2003; Morgane et al., 2002). Subsequently, this results in more inhibition of certain hippocampal regions, thereby potentially affecting information outflow and integration (Morgane et al., 2002).
Malnutrition results in deficits in long-term potentiation (LTP; Jordan & Clark, 1983), which is considered a candidate mechanism for learning and memory processes (Bliss & Collingridge, 1993; Kandel & Schwartz, 1982; Martin & Morris, 2002). Moreover, Morgane and colleagues (2002) stated that perturbations of hippocampal inhibitory mechanisms produce asynchronous activity of neuronal networks, potentially leading to decreased hippocampal plasticity (Morgane et al., 1993). Furthermore, Jordan and associates (Jordan, Howells, McNaughton, & Heatie, 1982) suggested that malnutrition induces changes at the level of hippocampal synapses. In summary, early malnutrition appears to disturb hippocampal function through a variety of mechanisms (Morgane et al., 2002).

Early PEM is associated with a reduction in dendritic spine density and with abnormal spine morphology in the hippocampus, cerebral cortex, and cerebellum (Benitez-Bribiesca, De la Rosa-Alvarez, & Mansilla-Olivares, 1999; Fiala, Spacek, & Harris, 2002). A dendritic spine is a plastic structure frequently found in the cortex and is thought to play an important role in stimulus encoding and information processing (Bonhoeffer & Yuste, 2002; Cos & Perkel, 1985; Fiala et al., 2002; Segal, 2001; Whittford et al., 2002). Specifically, malnutrition may result in anomalies of spine number and shape of pyramidal cells within cortical layers III and V and the CA3 region of the hippocampus and of granule neurons within the dentate gyrus (Fiala et al., 2002). Cerebellar granule cells, Purkinje cell spines, and giant spines are reduced in early malnutrition (Fiala et al., 2002). These findings are important because research indicates that dendritic spine abnormalities exist in conditions such as mental retardation (Fiala et al., 2002).

The previous discussion supports the assertion that early malnutrition can result in distinct changes in brain neurochemistry and delicate morphology (Almeida et al., 1996; Fiala et al., 2002). However, the process of brain development is likely significantly protected (through various homeostatic and placental mechanisms) from many harmful environmental influences. This being said, the developing organism can compensate only so much before long-term changes in the chemical composition or structural organization of the developing brain result. The precise nature and extent of these changes may vary among individuals, although some general patterns (such as elevation of neurotransmitter concentrations and pathological dendritic spine formation) likely exist.

Although specific pathological mechanisms explaining behavioral changes are unclear, developmental perturbations in neurochemistry, neurophysiology, and brain morphology resulting from early malnutrition implicate candidate mechanisms that could account for behavioral deficits. Research indicates that chronic changes in various neurotransmitter systems can affect levels of growth factors, gene expression, functioning of other transmitter systems, and the ability to acquire certain types of learning (Dudman et al., 2003; Kesslak, Chuang, & Berchtold, 2003; O'Donnell, Stemmelin, Nitta, Brouillette, & Quirion, 2003; Paule et al., 2003). Researchers have identified all of these factors as necessary components of typical CNS development (Acampora, Gulisano, & Simeone, 1999; Bar & Goffinet, 1999; Black, 1998; Cirulli, Berry, & Alleva, 2003; Cowan, 1998; Lyons et al., 1999; Nelson, 2000; Rutter & O'Connor, 2004; van Kesteren & Spencer, 2003). Therefore, significant or persistent dysfunctions in these systems (secondary to early malnutrition) may contribute to abnormal neurological development. Work by Gietzen and others (Blevins, Teh, Wang, & Gietzen, 2003; Gietzen & Magrum, 2001; Gietzen, Ross, Hao, & Sharp, 2004; Jousse et al., 2004; Truong, Magrum, & Gietzen, 2002) reveals that reductions of specific amino acids result in altered gene expression and changes in various neurotransmitter systems. These cascading effects provide a plausible mechanism for the effect of micronutrient malnutrition on neurobiology and behavior; that is, malnutrition causes decreases in important neurotransmitter systems, thus resulting in changes in growth factor concentration and in gene expression, eventually leading to modifications of behavior.

The discussion in this section focused on generalized caloric restriction/micronutrient deficiency. The reason for this emphasis is practical in that this is where many researchers have concentrated their efforts. However, as noted in the introduction, certain micronutrient deficiencies are associated with deviant brain development. Therefore, although little research exists directly linking specific micronutrient deficiencies to psychopathological outcomes, it is important to review briefly some of the extant research concerning the effect of specific micronutrient deficiencies on brain development.

PRIMER

As stated previously, it is common for deficits in micronutrients to accompany generalized protein energy malnutrition (Gorman, 1995; Kretchmer et al., 1996); conversely, it is possible to have deficits in specific micronutrients without concomitant caloric or protein restriction (Brozek, 1990; Georgieff & Rao, 2001). The latter scenario is more common in developed versus developing countries (A. S. Brown et al., 1996). As discussed earlier, A. S. Brown and colleagues postulated that deficiencies in specific mi-
Micronutrients (such as folate) more fully explain the findings in the Dutch hunger winter cohort. Numerous studies have repeatedly alluded early deficits of iron, zinc, and iodine with aberrant brain development and decreased cognitive skills; thus, this brief discussion focuses on these elements (Georgieff & Rao, 2001; Kretchmer et al., 1996; Yi-Ming, 1996).

Some studies have stressed the necessity of adequate levels of other micronutrients (such as vitamin B-6, selenium, manganese, copper, and choline) for proper neuronal development; however, they have been studied less extensively, especially with regard to human brain development and cognition (Castaño et al., 1997; Craciunescu, Albright, Mar, Song, & Zeisel, 2003; Fisher, Zeisel, Mar, & Sadler, 2002; Guilarte, 1989, 1993; Groziak & Kirksey, 1990; Keen et al., 1999; McCullough et al., 1990; Probaska, 2000; Watanabe & Sato, 1994; Yi-Ming, 1996; Zeisel, 2000). However, several studies have linked decreased periconceptional folate concentration to the development of neural tube defects in the progeny of some individuals (Czeizel & Dudas, 1992; Hibbard & Smithells, 1965). A. S. Brown et al. (1996) conjectured an association between prenatal folate deficiency and the development of schizophrenia. Furthermore, investigators have observed lower folate levels in depressed adults, but the etiology or significance of these reductions (i.e., if they represent a symptom of or a contributor to depression) is unknown (Alpert & Fava, 1997).

Iron

Iron deficiency (ID) is one of the most common forms of undernutrition in the world (Lozoff, 1989). It is caused by chronic malnutrition or consumption of foods low in dietary iron (usually the case in developing countries), or by conditions such as maternal diabetes or IUGR (usually the case in developed countries; Georgieff & Rao, 2001; Petry et al., 1992). A significant body of work has connected early ID to disturbances in myelination, neurotransmitter systems, metabolism, and hippocampal morphological development (Beard, 2003; de Deuengria et al., 2000; Jorgenson, Wobken, & Georgieff, 2003; Kwik-Urbie, Gietzen, German, Golub, & Keen, 2000; Lozoff, 1989).

Behavioral studies with animals have shown that perinatal ID results in impaired performance of hippocampally dependent tasks, lower environmental reactivity, and decreased motor skills (Felt & Lozoff, 1996; Schmidt, Waldow, Salinas, & Georgieff, 2004). Finally, studies conducted with ID infants and children have revealed deficits in motor skills, sensory processing, recognition memory, visuospatial abilities, language skills, attention, and academic performance—some of which may persist after iron repletion (Lozoff et al., 2003; Lozoff, Jimenez, Hagen, Mollen, & Wolf, 2000; Nelson, Wewerka, Borscheid, deRegnier, & Georgieff, 2003; Roncaglilo, Garrido, Walter, Peirano, & Lozoff, 1998; Stoltzfus et al., 2001). Lozoff and colleagues (2003) contend that ID children are less socially interactive, display more inefficient information processing, and exhibit reduced activity in their physical environment. Thus, they conjecture that ID infants are less likely to receive sufficient environmental stimulation. Although some researchers have indicated that ID children display more anxious/wrathful temperaments (Lozoff et al., 2003), no studies have expressly linked early ID to the later development of psychopathology.

Iodine

Iodine is a necessary component of various thyroid hormones. In the late 1990s, estimates indicated that approximately 1 billion people in the world were at risk for iodine deficiency (Yi-Ming, 1996). Severe maternal iodine deficiency in the preconception period (usually attributed to hypothyroidism) is associated with the development of severe mental retardation secondary to endemic cretinism (Pharaoh et al., 1971). Moreover, moderately iodine-deficient children display minor (but significant) increases in reaction time and decrements on neuropsychological measures of verbal information processing, attention, and visual-motor integration (Fenzi et al., 1990; Lombardi et al., 1995). These studies suggested that the differences were time-limited and amenable to amelioration with iodine therapy. Additionally, periconceptional injection of iodized oil in at-risk populations is effective in attenuating the incidence of endemic cretinism and subsequent mental retardation (Pharaoh et al., 1971). Conversely, prolonged childhood iodine deficiency may lead to lower achievement motivation and decreased learning speed, both of which become more striking with increasing age (Tiwari, Godbole, Chattopadhyay, Mandal, & Mithal, 1996). Again, no investigations have specifically examined any possible connections between early iodine deficiency and the development of mental illness (with the well-established connection between maternal iodine deficiency and mental retardation being the exception).

Zinc

Zinc is an important component of many enzyme systems and has been localized to presynaptic vesicles within limbic and cortical regions of the brain (Frederickson & Danscher, 1990; Johnson, 2001; Tuormaa, 1995). Zinc deficiency is associated with growth retardation and impaired hippocampal
functioning (Sandstead et al., 1998; Tuormaa, 1995). Zinc is also critical for axonal transport and proliferation during neuronal development (Tuormaa, 1995). Animals made zinc-deficient early in gestation commonly experience fetal reabsorption or spontaneous abortion (Tuormaa, 1995). Zinc deficiency in later gestation or during lactation results in decreased forebrain and hippocampal size as well as reductions in total cell numbers (Duaham & Russell, 1984; Tuormaa, 1995).

Some researchers have linked zinc deficiency to increased hyperactivity, apathy, lethargy, sleep problems, poor appetite, aggression, and irritability (Tuormaa, 1995). Others have hypothesized that maternal zinc deficiency during gestation results in permanent alterations of neurological development, which may eventually manifest as psychiatric or neurological conditions (such as Schizophrenia, Autism, epilepsy, and Parkinson’s disease; Johnson, 2001). Despite the potential seriousness of zinc deficiency, a study by Sandstead and colleagues (1998) reported that zinc-deficient children showed improved neuropsychological test performance after 10 weeks of zinc supplementation, leaving open the possibility of successful zinc rehabilitation.

**FUTURE DIRECTIONS**

The research reviewed in this chapter indicates that malnutrition is associated with disturbances in neurotransmitter systems necessary for normal neuronal maturation, morphological changes in delicate brain structures, and reductions in brain growth. Functional behavioral disturbances include deficits in cognitive abilities and an increased risk for psychiatric disorders, including Schizophrenia and related conditions such as externalizing behaviors and internalizing difficulties. These form and function effects persist across various models of malnutrition in animal studies and across demographic factors (country of origin and social class) in human investigations.

Isolating the specific role played by early malnutrition in the development of psychopathology in humans remains difficult because of multiple covariates. However, the problem of early malnutrition is significant for both developed and developing countries; thus, additional research is necessary to better explicate the long-term consequences of this condition. A major issue that future research should specifically address is the significance (i.e., magnitude of the effect) of malnutrition in the development of psychopathology. Specifically, does early malnutrition independently increase the risk for the development of psychopathology, or is it merely one of many important factors that, when combined, have a deleterious effect? The challenge lies in conjecturing plausible and testable mechanisms for these interactions and deriving maximally precise predictions of which factors contribute in which ways to the eventual outcomes. These are likely to be neurobiological models (concerned with cellular and molecular mechanisms) which then will inform behavioral models (tested on animals and concerned with negative correlates) based on extant relationships between form and function in the brain that are conserved across species. These studies would be complemented by statistical models that seek to explain population and subpopulation relationships among factors. Because criteria for the diagnosis of mental disorders is somewhat arbitrary and may be somewhat culturally determined, a possible way of examining this issue across settings may be to investigate more biological markers of mental disorders (such as dexamethasone suppression in depression). Although this particular test is far from perfect, this approach may provide a useful tool for examining the base rate of psychopathology in undernourished populations, where the current diagnostic system may be less effective for determining the presence or absence of a disorder.

The research reviewed supports the hypothesis that time of onset, dose, and duration of nutritional insults and interventions play critical roles in determining the nature and extent of any deficits (Morgane et al., 1993; Politt, 1996). What is not known is how much each of these three factors uniquely contributes to the eventual neurobehavioral outcome. Although there are no convincing animal models of psychopathology, animal studies designed to manipulate time of onset, dose, and duration of early malnutrition would help to explain the relative role of these components on neurochemistry, neuroanatomy, and some basic behavior (e.g., habit learning and recognition/spatial memory). Using neuroimaging and postmortem techniques, these findings could then be extended to human populations and, combined with evolving knowledge of the neurologic basis of psychopathology, may provide insight into the relationship between early malnutrition and the development of mental illness.

Overall, data indicate that specific micronutrient deficiencies can affect brain growth, cognitive development, and behavior. Nevertheless, adequate experiments explaining how deficits in these specific micronutrients result in the development of psychopathology (with the exception of mental retardation) have not been conducted. Examples of this approach include DNA microarray and proteomic and metabolomic assessments of targeted brain regions or processes (e.g., myelination, migration) following specific
timed nutrient deficiencies. The expectation would be to identify genes and gene products that mediate neuronal form and function. For example, studies investigating the hypothesized connection between prenatal folate deficiency, potential migration defects, and the later development of Schizophrenia could be addressed using such an approach. Studies of this kind are particularly important, given the significant number of individuals (in both developed and developing countries) affected by early micronutrient deficiencies, both apart from and in combination with generalized malnutrition.

Explaining how early malnutrition exerts negative effects on the developing nervous system is also a critical direction for future investigations. Possible neuropathogenic mechanisms of early malnutrition can be broken down into direct and indirect effects. Direct effects refer to those that are the primary result of malnutrition and are considered to underlie the subsequent pathology (e.g., disrupted neurotransmitter function, brain morphology, or myelination). These primary effects could potentially work through direct nutrient contact with DNA promoter regions (as seen with zinc) or at any other posttranscriptional regulatory sites. Indirect effects refer to effects that may potentiate other pathological processes or conditions associated with a pernicious outcome, for example, where the nutrient deficiency affects pregnancy integrity, maternal stress levels, or maternal parenting style. Other indirect effects could occur through nutrient deficiency effects on metabolism that in turn influence fetal programming of brain development. It should be noted that none of these mechanisms has been irrefutably linked to the development of psychopathology. They are merely presented here as possibilities to be considered; however, investigating all of these potential mechanisms would be fruitful grounds for future scientific inquiry.

Future research will need to take the knowledge gained at the regulatory level and apply it to physiologic studies at the systems level. For example, many studies have associated disturbances in various neurotransmitter systems (e.g., monoaminergic and glutamatergic) with psychiatric disorders, including Schizophrenia, depression, and anxiety (Fishbein & Pease, 1994; Kaufman et al., 2000; Konradi & Heckers, 2003). Furthermore, evidence indicates that early malnutrition (or deficiencies in micronutrients such as iron) results in alterations in the development and eventual functioning of certain neurotransmitter systems (Hernandez-Rodriguez & Manjarrez-Gutierrez, 2001; Manjarrez et al., 2003). Although it is difficult to speculate on a specific causative mechanism, prolonged increases in neurotransmitter concentrations yielding diminished receptor density or augmented neurotransmitter uptake may significantly alter the neurochemical milieu affecting the functioning of the entire nervous system (Almeida et al., 1996; Wauben & Wainwright, 1999). Additionally, some have postulated that neurotransmitter systems interact with each other during development (Benes et al., 2000); thus, perturbations in one system due to malnutrition may affect the developmental course of other systems (Wauben & Wainwright, 1999). For example, researchers have conjectured that changes in the glutamate, GABA, and norepinephrine systems interact with and contribute to the dysregulation of the dopamine system observed in Schizophrenia (Friedman, Temporini, & Davis, 1999; Goldman-Rakic & Selemon, 1997; Laruelle, Kegeles, & Abi-Dargham, 2003; Syvalahti, 1994). In addition, dysregulation of certain neurotransmitter systems may adversely affect dendrite formation, gene expression, and neurophysiological functioning (Gietzen et al., 2004; Jousse et al., 2004; Ma et al., 2000; van Kesteren & Spencer, 2003).

The hypothesized relationship between malnutrition and hippocampal dysfunction and between hippocampal dysfunction and psychopathology suggest that this circuit plays a role in the emergence of psychopathology following early nutritional deficits. As highlighted previously, researchers have connected early deficits of protein/protein energy, iron, or zinc to hippocampal malformation/dysfunction (de Deugdria et al., 2000; Jorgenson et al., 2003; Morgane et al., 2002; Schmidt et al., 2004; Tuormaa, 1995). This specific brain structure is noteworthy because it has been implicated in various types of psychopathology, including Schizophrenia, alcohol abuse, antisocial behavior, and anxiety/depression (E. S. Brown, Rush, & McEwen, 1999; De Bellis et al., 2000; Heckers et al., 1998; Heim & Nemeroff, 1999, 2001; Korbo, 1999; Korte, 2001; Laakso et al., 2000, 2001; Rajkowska, 2000). However, it is not known whether the hippocampus plays a direct causal role, if it modulates other structures involved in the pathogenesis of the disorder (e.g., frontal lobe structures), or if disruption in this region represents more generalized brain atrophy (Graham, Heim, Goodman, Miller, & Nemeroff, 1999). It is possible that, although affected, the hippocampus itself is not the crucial contributor to a deviant behavioral outcome. Rather, it is possible that hippocampal dysfunction disrupts projections to/from other brain structures, thus deranging the functioning of a wider cortical network.

Another effect of early nutritional deficits (specifically resulting from iron deficiency and essential fatty acid deficiency) is disrupted myelination (Kwik-Uribe et al., 2000; Roncagliolo et al., 1998). This is of note because researchers
have reported the occurrence of aberrant white matter structures in various psychiatric disorders (e.g., schizophrenia and mood disorders; Cotter et al., 2001; Davis et al., 2003; Molnar, Potkin, Bunney, & Jones, 2003; Öngür, Drevets, & Price, 1998). Again, the relationship between the observed white matter abnormalities and the behavioral phenotypes of the disorder are currently unknown; however, they deserve future scrutiny because it is conceivable that the white matter changes are causally linked to psychopathology (Jones, 1997).

Maternal stress is an example of a more indirect effect that may partly explain the role of malnutrition in the emergence of mental disorders. For example, more than likely, chronic malnutrition rarely occurs in the absence of significant maternal stress (Gorman, 1995). Therefore, malnutrition could potentiate the effects of maternal stress or vice versa. The pervasiveness of maternal stress during the Second World War makes it unlikely that this factor alone can account for the pattern of deficits observed in the Dutch famine studies. Nevertheless, maternal stress cannot be ruled out as a factor contributing (either additively or synergistically) to these findings. Similarly, malnutrition of the child or infant likely occurs along with malnutrition of the mother. Thus, as suggested by the studies of Keys and colleagues (Franklin et al., 1948; Keys, 1946), significant malnutrition affects the psychological functioning of the mother and presumably her ensuing interactions with her child. Therefore, some of the consequences observed following malnutrition could partly result from disordered mother-child interactions. The magnitude of this effect—indeed, of other environmental/biological influences—remains unclear (Moffitt & Caspi, 2001). However, if the maternal behavior is severely abusive or pathological to the point of being unable to provide the minimal physical, perceptual, and social stimulation required for normal brain development, then a deviant outcome compounded by malnutrition is likely (Guesry, 1998; Jaffee, Caspi, Moffitt, & Taylor, 2004; Raine, Brennan, & Mednick, 1994, 1997; Stein & Susser, 1985; Tully, Arseneault, Caspi, Moffitt, & Morgan, 2004).

Some researchers have suggested that the early intratuterine environment "programs" the fetus early in gestation (Barker, 2001). This mechanism is regarded as an adaptive response helping the fetus to react during gestation to particular stressors such as malnutrition (Barker, 2001; Oliver et al., 1999; Seckl, 1998). Proponents of this theory argue that these adaptive changes become liabilities when the environmental challenge is no longer present (Barker, 2001; Oliver et al., 1999; Seckl, 1998). Barker and colleagues (Barker, Forsén, Uutela, Osmond, & Eriksson, 2001) have invoked this fetal programming hypothesis to explain the relationship between retarded intrauterine growth and the later development of coronary heart disease. These researchers used the fetal programming hypothesis to explain their findings of a link between fetal undernutrition and the later development of depression (Thompson et al., 2001). Fetal programming in response to malnutrition could account for many of the descriptive findings regarding prenatal undernutrition; however, a precise mechanism for these alterations is still unknown (Seckl, 1998).

Another potential indirect effect connecting early malnutrition to the development of psychopathology is the decreased cognitive abilities observed in numerous studies. As discussed, research indicates that postnatal malnutrition can result in long-term reduction of intellectual abilities and cognitive skills (e.g., attention; Galler et al., 1986; Galler & Ramsey, 1987, 1989). These findings are important because intellectual ability measures obtained in middle childhood are highly stable into later life (Deary, Whalley, Lemon, Crawford, & Starr, 2000; Deary, Whiteman, Starr, Whalley, & Fox, 2004). Other research indicates that low intelligence is an independent predictor of lifetime psychiatric contact in that lower intellectual capacity results in a significantly increased risk for developing psychiatric difficulties, including conduct problems and antisocial behavior (Moffitt, Gabrieli, Mednick, & Schulsinger, 1981; Walker, McConville, Hunter, Deary, & Whalley, 2002).

Jacobs and others (2002) found that although childhood cognitive ability and childhood psychopathology are predicted by independent genetic factors, a third genetic factor along with (unspecified) nonshared environmental factors predicts both. Thus, if postnatal malnutrition results in decreases in IQ sustained through middle childhood, these are likely permanent and may in turn lead to increased psychiatric contact. These results may be subtle and relatively small on the individual level. However, slight perturbations in the population IQ will greatly impact the number of individuals classified as mentally retarded and requiring social support services, thus increasing the financial cost to society (Tanner & Finn-Stevenson, 2002). Moreover, reductions in population IQ and specific cognitive skills (such as verbal reasoning) may increase the number of individuals requiring psychiatric support services and engaging in impulsive/delinquent behaviors (Arseneault, Moffitt, Caspi, Taylor, & Silva, 2000; Moffitt et al., 1981; Stevens, Kaplan, & Bauer, 2001; Stevens, Kaplan, & Hesselbrock, 2003).

Finally, early nutritional deficits may make an individual more vulnerable to insults (such as hypoxia) that are as-
associated with the development of psychopathology (McNeil et al., 2000). Rao et al. (1999) provided some evidence for
this hypothesis by showing that prenatally iron-deficient juvenile animals sustained more damage to the hippocampus following a hypoxic ischemic insult. Moreover, Fechner and colleagues (2001) showed that children admitted to hospital suffering from kwashiorkor exhibited decreased plasma antioxidant levels. Decreased antioxidant concentrations likely make these children more susceptible to neuronal damage/death after traumatic injuries such as anoxia or hypoxia-ischemia (Buonocore, Perrone, & Bracci, 2001; Zauner, Daugherty, Bullock, & Warner, 2002).

Similarly, compared to well-nourished children, malnourished children are more susceptible to cell damage and exhibit decreased DNA repair following an injury (Gonzalez et al., 2002). Gietzen and colleagues (1996) observed that rats with essential amino acid deficiencies displayed heightened seizure vulnerability. Research suggests that maternal zinc deficiency exacerbates the effects of prenatal alcohol exposure (Flynn et al., 1981).

These findings suggest that a nervous system already compromised by malnutrition is more vulnerable to additional insults such as toxin exposure or chronic stress. As discussed in the section on neurobiology, there is a potential for malnutrition or any early stress to alter the fundamental organization or structure of the developing brain. Although these modifications may prove beneficial in the short term (e.g., by conserving energy or reallocating resources), they may prove detrimental in the long term, possibly by decreasing behavioral and/or cellular plasticity (Barker, 2001).

Thus, malnutrition may serve as a catalyst disrupting normal development, but it may not have an enduring effect unless occurring proximally with another insult. Furthermore, the consequences of early malnutrition may not be revealed until a future stressor tries the plasticity of the system. This model is analogous to the diathesis-stress theory of mental disorders. In this model, undernutrition could be the stress (second injury), and the diathesis (initial damage) could stem from a genetic vulnerability or from other, already present environmental risk factors. Conversely, early malnutrition and its effects could be present first, so that a later infection, toxin exposure, or hypoxic/ischemic event would tip the scales toward an undesirable outcome. As discussed in the introduction, another variable to consider in this system is an individual's ability to maintain homeostasis in response to a challenge. This model may explain some of the discrepant findings in the literature. That is, it posits that each individual has his or her own threshold of how much damage via malnutrition (or other environmental insults) he or she can endure before exhibiting an aberrant phenotype. It also hypothesizes that malnutrition exerts its maximal effect if it occurs in the context of an already compromised system. Again, this is merely a hypothesis and it should be rigorously tested (including the formulation of models that strive to describe this threshold in terms of numerical relationships and which factors are the best predictors of eventual outcome).

The question is not whether severe malnutrition (i.e., starvation) leads to adverse outcomes, because it is obvious that beyond a certain threshold of caloric restriction, conception becomes unlikely, miscarriage is inevitable, and death eventually results if adequate energy intake is not restored (Coad, Al-Rasasi, & Morgan, 2002; King, 2003; Stein et al., 1972). Rather, the question that future research should address is: Given a limited supply of energy, protein, or specific micronutrients, is an individual at an increased risk for developing psychopathology? Complicating the picture, available research suggests that generalized malnutrition rarely exists without micronutrient (iron/zinc) deficits, decreased parental intellectual abilities, deficient psychosocial stimulation, chronic childhood illness, or unsanitary living conditions (Guesry, 1998; Ivanovic et al., 2002; Pollitt, 1969; Stein & Susser, 1985). Even in the case of the Dutch hunger winter, the population was not free from significant wartime- and famine-induced stress. Therefore, it is difficult to discern if there is a unique contribution of early malnutrition to the development of psychopathology, and what, if any, is the relationship between malnutrition and other risk factors (i.e., mediational, additive, or synergistic).

Early malnutrition appears to be a topic very well suited to a multidisciplinary approach that includes basic science (neurobiology and biochemistry) as the foundation, translational research (such as using animals to model various paradigms of malnutrition), and finally comprehensive human investigations which include measures of motor, perceptual, cognitive, and intellectual abilities as well as objective measures of personality and psychopathological symptoms. These human studies should also endeavor to match participants or otherwise statistically control for potential confounds such as SES, parental education/IQ, familial history of mental illness, toxin exposure, and living circumstances. Although costly and difficult to conduct, a human study incorporating all of these components would provide valuable data that would greatly augment our understanding of the long-term effects of early malnutrition and specify how this condition interacts with other risk factors.

The potential for interactions may explain the relative effectiveness of nutritional intervention programs in
developing countries compared to the often modest benefits shown by similar endeavors in countries such as the United States (Pollitt, 1996). That is, in developing countries, the population is likely to be chronically undernourished but may not exhibit elevated rates of psychopathology, and parents might provide a stable home environment. Conversely, in developed countries, individuals at risk for early malnutrition are more likely to have genetic and additional environmental risk factors, increasing their chance of expressing a deviant phenotype. This is merely a speculation and is not intended to minimize the potential impact of early malnutrition or the need to address this issue, but rather to emphasize the idea that many malnourished children (especially in developed countries) possess other substantial risk factors such as poverty, unstable home environments, deficient psychosocial stimulation, and genetic propensities, which may complicate intervention efforts. Again, designing efficient, beneficial interventions is another area that future studies should explore. Implementing successful interventions in countries such as the United States will likely entail carefully designed, targeted procedures (such as ensuring proper prenatal care and nutrition, encouraging breast feeding and parental involvement, better parental and childhood nutrition education, proper vaccinations and postnatal nutrition) that begin early and aim to treat the gestalt of the circumstances and not merely a single destructive component of the milieu (Ramey & Ramey, 1998).

REFERENCES


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