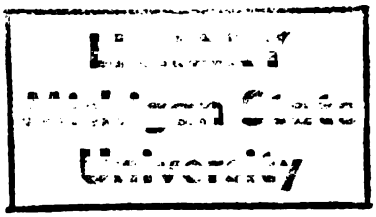

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ETIOLOGY AND PROGNOSIS FOR FIVE YEAR OLD CHILDREN WITH HEMORRHAGIC ENDOVASCULITIS OF THE PLACENTA

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Lori Ellicott

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Lawrence W. Lyatte
Major professor

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ETIOLOGY AND PROGNOSIS FOR FIVE YEAR OLD CHILDREN WITH HEMORRHAGIC ENDOVASCULITIS OF THE PLACENTA

By

Lori Ann Ellicott

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ABSTRACT

ETIOLOGY AND PROGNOSIS FOR FIVE YEAR OLD CHILDREN WITH HEMORRHAGIC ENDOVASCULITIS OF THE PLACENTA

by

Lori Ellicott

Five year old children with hemorrhagic endovasculitis (HEV) of the placenta were examined on various outcome measures with the objective of determining the nature and extent of sequelae for liveborn children with this placental lesion. Prior studies had found significant associations with stillbirth, small for gestational age, and maternal hypertension or pre-eclampsia. In light of these risk factors, it was hypothesized that HEV children might be at risk for later problems. Thus, the study set out to assess the relationship of various pre-, peri-, and postnatal factors with sequelae.

The study consisted of examining medical records to assess the health status of mother and infant, and assessing the children on the following measures: The McCarthy Scales of Children's Abilities, Bender Visual Motor Gestalt Test, Personality Inventory for Children-Revised, and Dimensions of Temperament Survey-Revised. Maternal interviews elicited demographic and health and pregnancy information.

Two control groups, matched on birth date and location, were used in the design. The Registry control group consisted of children with a variety of pregnancy and/or birth complications but not HEV. The community control group was comprised of healthy, term

infants.

Significant confounding variables included chronic villitis and maternal hypertension. Presence of chronic villitis was significantly associated with increased difficulties on the personality measure across groups. Presence of maternal hypertension significantly correlated to increased approach behavior. Additionally, for the HEV group, presence of maternal hypertension correlated to several dimensions of more difficult temperament. Increased rates of abnormal scores for the HEV group were noted when chronic villitis, hypertension, or both were present.

It appears that children with HEV affected placentas are at risk for poorer prognosis at five years of age, particularly in the face of chronic villitis or hypertension. However, children with chronic villitis of the placenta and/or presence of maternal hypertension regardless of group membership are at increased risk for personality and temperament difficulties at five years of age.

To my husband Vern and daughter Christine whose love, support, and laughter have warmed me.

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CHAPTER I

Importance of the Study

Hemorrhagic Endovasculitis (HEV) is a recently identified abnormality of human placentas (Sander, 1980). This lesion focuses on placental blood vessels, destroying fetal red blood cells and causing hemorrhage within the placenta. Since its initial discovery in 1977 at the Michigan Placental Tissue Registry (see Appendix A) nearly 20% of the Registry's placentas show some degree of HEV. In a review of 218 HEV affected placentas, Stevens (1984) found 51% (112/218) associated with stillborn infants in contrast to 22% (89/400) of the Registry control placentas. The Registry control placentas had various pregnancy, delivery, and/or placental abnormalities, but not HEV. Additionally, liveborns with HEV affected placentas were significantly smaller for gestational age (33% to 19%, using a criterion of weight less than the 10th percentile for gestational age) and were more likely to be female (57% to 48.4%) than were Registry controls. (Infants who are small for gestational age, or sga, are inadequately grown for their gestational age. Both preterm and fullterm infants comprise this group.) Other significant positive associations with HEV included later gestational age, smaller placentas, and maternal hypertension

or pre-eclampsia. No association was found for maternal age, race, parity, infant Apgar score or fetal anomalies. The prevalence of HEV in the general population is not known at this time.

The focus of research in this area has been largely on stillborn cases and placental pathology in both liveborn and stillborn infants. Thus there is a strong need to investigate liveborn children with HEV affected placentas particularly in light of later sequelae stemming from the early risk factors of maternal hypertension or pre-eclampsia and small for gestational age.

A pilot study to begin assessing children with HEV affected placentas was initiated in 1983. The original cases of children with HEV affected placentas identified in 1977 were located and assessed on cognitive and personality scales at approximately five years of age. Fourteen of the original 17 children were available for follow up. They were matched on birthdate and location to a Registry control group of children. Results of a paired t test found the General Cognitive Index on the McCarthy Scales of Children's Abilities to be significant ($p < .01$). This indicated that children with HEV affected placentas preformed poorer on this summary measure of cognition than their matched controls. Additionally, the children with HEV affected placentas exhibited more extreme scores on personality indices. However, the differences were not statistically significant.

Statement of Purpose

It is the purpose of this study to follow up children with a specific placental abnormality identified as hemorrhagic endovasculitis (HEV) on various measures of perception, cognition,

temperament, personality, and health and physical status. The children will be assessed at approximately five years of age.

The outcomes of the children with HEV affected placentas will be compared to those of a community control group and a Registry control group. The outcome variables will be statistically examined so as to identify the nature, incidence, and severity of sequelae for the HEV children. Particular attention will be given to factors in the pre-, peri-, and postnatal environments associated with poorer outcomes.

Background of Theory and Research

Several theories pertain to this study. Foremost are the contrasting continuums of reproductive casualty and caretaking casualty posited by Pasamanick and Knobloch (1961) and Sameroff and Chandler (1975) respectively. These theories address the issue of a linear (predictive) relationship between perinatal history and outcome.

The continuum of reproductive casualty suggests a relationship between certain harmful events of pregnancy and delivery which result in damage to the fetus or neonate primarily localized to the central nervous system. The lethal events on the continuum are evidenced in abortions, stillbirths, and neonatal death, whereas the sublethal components result in cerebral palsy, epilepsy, mental retardation, and behavioral and learning disorders. Evidence for the continuum of reproductive casualty largely has come from retrospective studies which have implicated anoxia (also referred to as asphyxia or hypoxia in the literature; its presence indicates a reduction in oxygen level below the requirements of the organism),

prematurity, delivery complications and social factors in eventual outcome (Knobloch & Pasamanick, 1966; Pasamanick & Knobloch, 1961, 1966; Pasamanick & Lilienfeld, 1955).

In contrast to this is the continuum of caretaking casualty noted by Sameroff and Chandler (1975) with its largely prospective focus. The authors argue that certain pregnancy and/or birth complications are recognized as affecting newborn behavior and intellectual functioning through the preschool period, but these deficits are greatly reduced as the child enters school. Moreover, social and economic factors tend to either reduce or amplify these deficits, leading to the conclusion that social and economic factors in the child's environment exert stronger influences on the course of development than does perinatal history. Substantiating this point of view is the observation that many children suffering perinatal problems have normal developmental outcomes. Thus, a transactional model where the child and environment mutually influence each other was felt to be necessary to understand outcomes. To the extent that the child elicited or was provided with a positive environment, enhanced outcomes resulted. Conversely, when a child elicited negative responses from the environment, the child was at greater risk for the development of later problems (Sameroff, 1975; Sameroff & Chandler, 1975; Sameroff & Seifer, 1983).

A third theory pertaining to this study centers around the etiology of HEV and its implications for developmental sequelae. Sander (1980), notes that many features of HEV simulate the placental response to some viral infections that may occur during

pregnancy. The most suspect infectious agents are of the TORCH group (which includes toxoplasmosis, rubella, cytomegalovirus, syphilis,and other infectious agents). The literature is suggestive of a wide range of effects from perinatal viral infections, including fetal death, intrauterine growth retardation, stillbirth, death in infancy, congenital anomalies (referring to any abnormality present at or detectable immediately after birth resulting from such perinatal environmental insults as infectious agents or teratogens), late onset of congenital disease or defects, infections without evidence of damage, and no apparent damage (Hanshaw & Dudgeon, 1978; Sever, 1970). The precise nature of the fetal damage is suggested to vary depending on the type of infectious agent, the gestational age at which the infection occurs, and the nature of the transmission from mother to fetus.

The point of departure for this paper will be to examine the relationship of HEV's infectious association with the continuums of reproductive and caretaking casualty. Thus the factors in the pre-, peri-, and postnatal environments will be examined in light of outcome measures, with the goal of delineating those factors that are associated with performance at five years of age.

Limitations of the Study

There are several sources of bias affecting this study. Among them are the effects of migrator bias. It may well be that children unavailable for follow up due to moving outside the geographic scope of this study may have differed systematically from those who remained within the parameters of the study.

Recall bias is another source of potential confound. Mothers

may have recalled only certain aspects of their pre-, peri-, and postnatal health status while omitting some relevant details. However, this is minimized somewhat by the use of medical records to supplement maternal reports. Further confounding this was the maternal interviewer's knowledge regarding the status of the subjects. The interviewer for the mothers may have held diagnostic suspicions or expectations which influenced the intensity with which a question was asked of the mother, the number of repetitions of a question, depth of pursuit or inquiry, or systematic errors in recording results. This problem was lessened by utilizing interview schedules (see Appendix C).

One pathologist is responsible for identifying presence of HEV of the placenta at the Registry. This is a strength in consistency but examiner bias becomes an issue. However, this is somewhat minimized due to a series of slides sent to other pathologists who have concurred with the original findings.

Chapter Summary

This chapter has attempted to delineate the scope of the study to follow. Specifically, it has identified children with HEV affected placentas as being the target population. It was noted that HEV is a recently discovered placental abnormality in need of investigation regarding sequelae in liveborn children. An association with viral infection has been noted by Sander (1980). Sequelae at five years of age with various pre-, peri-, and postnatal conditions will be the subject of inquiry in the ensuing study.

CHAPTER II

Review of Related Literature

The ensuing review of literature will progress from postulated mechanisms of HEV to a review of related outcomes. Since chronic villitis (a chronic inflammation within placental villi due to a variety of infectious agents) and sga infants are both significantly associated with HEV (60% and 33% respectively, Stevens, 1984), these areas will be examined in some depth. The chapter will begin with an examination of placental pathology and viral infections since the latter have been suspect in the etiology of HEV. A discussion of the etiology of intrauterine growth retardation will follow. Classification systems for fetal growth retardation will be surveyed, concluding with a review of prognosis for sga infants.

Placental Pathology and Viral Infections

The well being of the newborn infant depends not only on its genetic endowment, but also on its mother's health and management through pregnancy and birth. Thus, the role of the placenta in maternal and fetal welfare is attracting increased attention. Abnormalities of the placenta have been associated with an increased incidence of abortion, prematurity, stillbirth, bleeding in pregnancy, and intrauterine growth retardation, the latter of which

is relevant to the study at hand (Altshuler, Russell, & Ermocilla, 1974; Scott & Usher, 1966). Despite the high incidences of mortality and morbidity associated with placental pathology, the placenta has been a largely neglected organ for investigation when compared to other organs of the human body. Part of this neglect stems from the economic and time constraints faced by obstetricians, pediatricians, and pathologists. Since it is impractical to examine all delivered placentas, those submitted tend to be of the stillborn or critically ill newborn. Thus there tends to be very little information about the placenta in relation to many conditions, including two fairly common viral infections; rubella and cytomegalovirus disease (CMV) since infants tend to survive the neonatal period in the case of the former, and in the latter instance most infections are not apparent.

As a diagnostic intrument representing fetal and maternal tissues, the placenta can be useful in identifying the presence of infectious agents. Such was the case with rubella, where the first clue that the fetus could become infected from maternal rubella came from joint examination of the placenta and fetus (Hanshaw & Dudgeon, 1978). The placenta is similarly useful in evidencing CMV infection in the fetus or neonate, however, unlike rubella, the placenta is one of several modes of transmission of this disease. CMV is currently acknowledged as being the leading cause of congenital infection, surpassing even the rubella virus (Griffiths, Campbell-Benzie & Heath, 1980).

Viral infections have been implicated in poor fetal and infant outcome for some time. Damage may take the form of intrauterine

growth retardation, stillbirth, infant death, or mild to severe forms of congenital defects (Jones & Roberton, 1984). There may also be no incidence of damage. Outcome is suggested to depend on the type of infectious agent, the gestational age at which infection occurs, and the route by which the agent is transmitted from mother to fetus or neonate (e.g. breast milk, placenta, respiratory route, sperm, etc.).

Chronic Villitis

Approximately 60% of HEV affected placentas show chronic inflammation within villi, or chronic villitis compared to a 20% overall incidence in Registry specimens (Sander & Stevens, 1984; Stevens, 1984). This is a non-specific response to a variety of infectious agents, in particular those of the TORCH group. Viral type intranuclear inclusion bodies have been found in 10.23% (71/694) of HEV affected placentas from 1978 to 1980. Excluded were nine placentas with CMV inclusions associated with known intrauterine CMV infection. The majority of HEV placentas evidencing chronic villitis have no known etiology.

Villitis of Unknown Etiology (VUE). In most instances chronic villitis is of unknown etiology. It is suggested that this lesion is many times more common than placental toxoplasmosis, CMV, rubella, syphilis and herpes infections combined (Russell, 1980). Studies have failed to reveal any etiologic agent, specifically excluding the TORCH agents (Altshuler et al., 1974). It is implicated in the etiology of intrauterine growth retardation, as shall be evidenced in a subsequent section.

There are several studies investigating VUE. The various

studies come to slightly different conclusions. For example, Altshuler et al. (1974) believe that placental infection is the cause of VUE; a conclusion drawn in part from evidence of intrauterine infection in some of the cases. This differs somewhat from the view of Labarrere, Althabe, and Talenta (1982) who postulate an immunological origin (which often is in response to a viral agent) similar to that postulated in placentas of pre-eclamptic pregnancies wherein the maternal immune system attacks the placental tissue. Russell (1980) notes that VUE is probably not a single, circumscribed, and easily defined entity that responds to only one organism. He notes that there are no obvious signs of intrauterine infection in the majority of neonates and so argues for a local source of infection in most instances. The absence of infection in mothers and infants are seen as attesting to this conclusion. Knox and Fox (1984) suggest that ethnic, environmental and socio-economic factors affect the incidence of villitis. They caution against assuming that all villitis are of infective origin, despite the documentation that many specific maternal infections (e.g. rubella, toxoplasmosis, etc.) can cause a villitis.

In short, it seems that the infectious origin (whether it be local, infecting only the placenta; evidenced in the mother or neonate; or an abnormal immune response) is the predominant view for the etiology of VUE. However, in the absence of identification and isolation of an infectious agent, this view remains inconclusive.

Congenital CMV Infection. Several studies have investigated the sequelae of CMV infection. It will be noted here due to its association with chronic villitis and its incidence in a small

percentage of HEV affected placentas identified between 1979 and 1982. Nine examples of chronic villitis associated with CMV have had coexistent HEV (Sander & Stevens, 1984).

CMV infection has been shown to cross the placenta and infect and damage the developing fetus. An incidence of 0.5% to 2.4% has been noted, with an increased incidence being noted in the lower socio-economic classes (Griffiths et al., 1980; Hanshaw, Scheiner, Moxley, Gaev, Abel & Scheiner, 1976; Keirse, 1984; Marx, 1975). Spread of the virus is facilitated by crowding and lack of sanitation facilities (Marx, 1975). In a study of neonates with clinical evidence of congenital CMV infection, 35-50% are sga (Allen, 1984). Pass, Stagno, Myers and Alford (1980) point out that 10% of infants in this country acquire CMV during the first year of life, however Marx (1975) states that acquiring the infection after birth has minimal effects. At present, there is no treatment for CMV infection nor a vaccine to prevent it.

The sequelae for congenital CMV infection is a wide range of clinical manifestations. Mortality rate for children with symptomatic congenital CMV infection varies from six to 30% (Allen, 1984). It is noted to be the most common viral cause of mental retardation, surpassing even the rubella virus (Marx, 1975; Pass et al., 1980). Significant hearing impairments have been noted in these children (Griffiths et al., 1980; Hanshaw et al., 1976; Melish & Hanshaw, 1973; Pass et al., 1980) as have higher than expected incidences of rare opthalmological abnormalities (Frankel, Keys, Hefferen, Rola-Pleszczysnki & Bellanti, 1980; Pass et al., 1980). Microencephaly, neuromuscular disorders, minimal brain dysfunction,

lower IQ scores and school failure are also among the clinical manifestations of congenital CMV infection (Griffiths et al., 1980; Hanshaw et al., 1976; Marx, 1975; Melish & Hanshaw, 1973; Pass et al., 1980). Keirse (1984) notes that about 90% of infants with CMV infection have no clinical manifestations at birth but some may reveal some developmental abnormalities by two years of age. Some degree of growth retardation occurs in approximately 40% of infants who reveal clinical manifestations of infection at birth.

Many factors may be associated with the clinical outcome of the virus, including gestational age at the time of infection, sex of the fetus, and individual differences in host susceptibility (Hanshaw, 1973; Kumar, Gold, Jacobs, Ernhart & Nankervis, 1984). However, the general conclusion in the reviewed studies appears to be that children with congenital CMV infection are at increased risk for handicaps that will significantly impair normal development.

Summary

It was pointed out that the placenta is useful as a biopsy specimen for identifying the presence of infectious agents in fetal and maternal tissues. Potential outcomes of viral infections were noted and the role of chronic villitis of both known and unknown etiology were reviewed as they pertain to a presumed infectious origin. It was found that the TORCH group is implicated in chronic villitis where infection can be identified, but there is presently a lack of evidence to implicate any viral agents (TORCH or others) as being causative in VUE with any certainty. However, due to the known response of chronic villitis to the TORCH agents, viral infections continue to be suspect in the etiology of VUE by a number

of pathologists despite the aforementioned problem. Thus the implication is that if VUE is a response to viral infections, then the clinical manifestations of children with VUE might be expected to resemble such sequelae as is noted for rubella or congenital CMV infections and other agents. This has implications for 60% of the HEV children whose placentas had signs of chronic villitis.

The reviewed literature suggests the importance of examining the association of chronic villitis and congenital viral infection to sequelae in our study. The increased incidence of chronic villitis and congenital infection among children with HEV affected placentas leads us to expect poorer results on various outcome measures for this group.

Etiology of Intrauterine Growth Retardation

Thirty three percent of HEV affected placentas are associated with sga births. SGA children are a distinct group born either preterm or fullterm who are markedly underweight for their gestational age and thus intrauterine malnutrition is presumed (Caputo & Mandell, 1970). Therefore it may be helpful to survey some of the known factors associated with delayed fetal growth. We should note at the onset that the definition of IUGR is far from uniform. Various criteria have been used, including the third or fifth or tenth percentiles, or two standard deviations from the mean on differing growth curves. (This study has used the Colorado Intrauterine Growth Chart to determine the presence of IUGR in the study subjects - see Appendix B.) Different labels are used interchangeably to denote this group of children, including small for date (sfd), small for gestational age (sga), intrauterine growth

retardation (IUGR), fetally malnourished, low ponderal index (low PI), and growth retarded infants. An incidence of two to ten percent of IUGR (below the tenth percentile) is noted in the general population (Douglas, 1982; Norman, 1982).

In addition, there is evidence suggesting that mothers whose first baby was sga have a three times higher risk of their second infant being sga than the population as a whole. This seems to indicate that a number of factors which retard fetal growth have a high recurrence rate (Keirse, 1984).

Placental Conditions

The placenta has been implicated in various ways in IUGR. For example, Altshuler et al. (1974) note an incidence of 92% (N=63) of gross and/or microscopic placental lesions in their sga subjects. Forty percent of the placentas evidenced circulatory disturbances, and 64% of this group (or 16 of 25) had pre-eclampsia of pregnancy. The role of maternal vascular disease (which includes hypertension, pre-eclampsia, antepartum hemorrhage, diabetes mellitus and chronic nephritis) has been further investigated in studies by Sheppard and Bonnar (1980) and DeWolf, Brosens, and Renaer (1980). The former study investigated 25 normal pregnancies and 25 pregnancies complicated by IUGR (birth weight below the fifth percentile for gestational age) and found evidence suggesting that lesions in the maternal uterine vasculature may be the major cause for impairment of placental function, marked by degenerative changes in placental villi. The conclusion of maternal origin is arrived at since fetal capillaries and blood cells appear structurally normal. These findings are similar to the study of five IUGR infants (below the

tenth percentile for gestational age) by DeWolf et al. (1980) who found that maternal vascular lesions in the placenta impaired blood flow and resulted in infarction and IUGR. The cause of the vascular lesions are unclear. However the possibility that underlying latent hypertensive or renal vascular disease may be the cause of the lesions in the placenta, for which fetal growth retardation is the first clinical manifestation is posited. The severity of maternal vascular disease, and hypertension in particular, was not seen as being correlated to the degree of IUGR.

Chronic villitus of unknown etiology (VUE) has been the subject of several studies investigating IUGR. In a study by Labarrere et al. (1982) the authors examined seven or eight sections of the placenta and found a very high incidence of chronic villitis in both the sga group (less than the tenth percentile on the ponderal curve) and in the normal control group (86% and 26% for the sga group and controls respectively). Ten percent of villi within each placenta were inflamed in the sga group compared to 1.2% in the control group. In contrast to these findings, Altshuler et al. (1974) found an incidence of 24% of VUE with sga infants (less than the tenth percentile for gestational age). Russell (1980) found that VUE was associated with IUGR and that the severity of the villitis process correlated positively with degree of IUGR and perinatal mortality.

Some additional placental characteristics have been associated with IUGR. For example, the absence of one umbilical artery has been implicated in fetal growth retardation as has smaller size of the placenta. However in the latter case where smaller fetuses are

observed to have smaller placentas, it is not certain what is cause and what is effect (Miller, 1983). Additionally, microscopic studies suggest that placentas of sga infants may receive insufficient oxygen, suggesting that the cause of fetal growth retardation is not placental damage, but restricted blood flow from the mother, which has implications for a restriction of nutrient transfer as well. Placenta previa has been shown to retard all parameters of fetal growth depending on the frequency and duration of bleeding (Crawford, 1982). Placental metabolism is also critical in supporting a pregnancy. Animal studies point out that the placenta consumes a major portion of the nutrient supply provided by the mother; up to 50% of the oxygen and 75% of the glucose put into uterine circulation by the mother in fetal lambs (Miller, 1983).

Maternal Factors

Various maternal characteristics have been associated with IUGR. Some of these have been previously mentioned which affect the placenta. These include the various vascular diseases (pre-eclampsia, antepartum hemorrhage, hypertension, diabetes mellitus, chronic nephritis). In one way or another, these conditions are thought to interfere with the nutrition of the infant (Chamberlain, 1984; Dawkins, 1965; Galbraith, Karchmar, Piercy, & Low, 1979; Keirse, 1984; McDonald, 1965; Schutt, 1965; Tejani, 1982). Intrauterine infections of the TORCH group are also implicated in IUGR, as has been previously noted.

Maternal habits, such as smoking, alcohol, and drug abuse are well documented correlates to fetal growth retardation. Smoking impairs both fetal length and weight and has been reported to cause

an increased rate of spontaneous abortion, prematurity, abruptio placenta, placenta previa, and premature rupture of the membranes. All growth parameters are affected when the mother is a heavy smoker (greater than 15 cigarettes a day) and the number of cigarettes per day has been shown to relate directly to the degree of growth retardation and to the incidence of prematurity. When smoking occurs in the presence of other known growth retarding factors, the result is more than additive (Chamberlain, 1984; Crawford, 1982; Keirse, 1984; Norman, 1982).

Excessive ingestion of alcohol by pregnant women has lead to the identification of a pattern of physical malformations in the offspring known as fetal alcohol syndrome or FAS (Abel, 1980). FAS is noted by a distinct pattern of congenital malformations which includes microcephaly, shortened palpebral fissures (the size of the eye opening) and joint, limb, and cardiac anomalies. Additionally, most of the affected infants are growth retarded in both length and weight (Abel, 1980; Clarren & Smith, 1978; Norman, 1982). Fetal weight may be reduced as much as 1200 grams. The influence on growth begins in the first half of pregnancy and continues into postnatal life (Keirse, 1984). Whether these effects are the direct result of alcohol or due to conditions secondary to alcohol intake (e.g. altered nutrition) is inconclusive at this time (Robertson, 1983).

Alcohol consumption does not necessarily lead to the FAS. Studies have linked heavy drinkers (greater than 45 drinks per month) to weight, length, and head circumference below the tenth percentile, despite not evidencing FAS (Keirse, 1984).

A high incidence of IUGR occurs with chronic heroin addiction as well. However, since other growth retarding factors frequently accompany drug abuse, it is uncertain whether fetal growth retardation results from the drug itself, from secondary factors or from a combination of these (Crawford, 1982).

Chronic maternal disease is frequently noted to result in IUGR. Such conditions as cyanotic congenital heart disease, advanced diabetes, and renal and gastrointestinal disease have been implicated (Crawford, 1982).

Multiple gestation is similarly noted to frequently result in fetal growth retardation and is most common in monozygotic twins. Intrauterine crowding and limited nutrient supply are among the possible causes. This may be compounded by such conditions as a small uterus or pelvis, or presence of tumors or ovarian cysts which further inhibit fetal growth, whether it is a multiple or single gestation (Crawford, 1982; Galbraith et al. 1979; Kopp & Parmelee, 1979; North, 1966).

Various chromosomal and congenital anomalies have been associated with IUGR (Collins & Turner, 1971; Crawford, 1982; Schutt, 1965). Among these are Trisomy 18 and 4p (short arm deletion). Trisomy 21 (Down's syndrome) infants are affected to a lesser degree, as are infants with sex chromosome abnormalities. Congenital anomalies have been noted to be of higher incidence among very low birth weight infants (less than 1500 grams) and among the premature sga infants.

Socio-economic Factors

Socio-economic factors have long been associated with IUGR and poorer fetal outcome in general (Sameroff, 1975; Sameroff & Chandler, 1975). For example, the lower classes are less likely to receive prenatal care or adequate nutrition during their pregnancy (Drillien, 1970). Women of low socio-economic status are more likely to adopt practices that adversely affect growth, such as drug or alcohol use or smoking. However if they did not adopt such practices, these women were no more likely to have infants with lower birth weights than women in other socio-economic groups (Keirse, 1984).

Amongst mothers of low socio-economic status, there tends to be a higher incidence of various complications of pregnancy, including antepartum hemorrhage and toxemia (Caputo & Mandell, 1970; McDonald, 1965). Increased rates of family instability and unemployment as well as minority group membership are often found in lower socio-economic classes as well. Thus, a multiplicity of stressors in the prenatal environment may have their effect in poorer prognosis at birth and in subsequent development, as shall be discussed later.

Summary

The primary mechanisms postulated to produce fetal growth retardation include impairment of oxygen and nutrient transport which are activated in a variety of ways, including conditions affecting: 1) the placenta (e.g. vascular disease, chronic villitis, placenta previa, placental metabolism); 2) maternal factors (e.g. habits such as smoking, alcohol and drug use; intrauterine infection, chronic disease, multiple gestation); and

3) socio-economic factors (e.g. inadequate nutrition, increased incidences of pregnancy complications, minority group membership, family and environmental stressors).

A number of potential confounds have been pointed out in the preceding section which will be measured in this study in order to understand group differences on the various outcome measures. Factors of interest include the presence of maternal disease (such as hypertension, diabetes, and pre-eclampsia or toxemia), smoking, alcohol consumption, drug use, multiple gestation, race, and income. All of these factors are associated with fetal growth retardation and poorer prognosis for the child. Since the HEV group has a higher incidence of IUGR (Stevens, 1984), this study expects to find increased incidences of growth retarding factors and poorer outcomes for this target group of children.

Classification Systems for Fetal Growth Retardation

Various means of classifying the fetally malnourished infant have been devised. The most common involves an examination of birth weight by gestational age and comparing this to a particular growth curve (Lubchenco, Hansman, Dressler & Boyd, 1963; Yerushalmy, 1967). However, disparty is still common even amongst these methods. For example, some curves include all births, others exclude stillbirths, multiple births or both. Some include only gestations known with certainty, while others include approximations or estimations of gestational age. In some, gestational age means completed weeks, or zero to six days, while others consider it to mean plus or minus three days (Keirse, 1984). Various criteria have been used to designate the sga infant; typically the third, fifth, or tenth

percentile, and most commonly the latter. The ensuing discussion will highlight other means for denoting these inadequately grown infants.

Keirse (1984) points out the existence of important differences between birth weight standards which relate to racial, genetic, socio-economic and environmental factors in the various growth curves. This points to the strong need to select standards which were obtained on a population that is similar to the one under study.

The ponderal index (PI) is perhaps the next most commonly used method for classifying inadequately grown infants after birth weight by gestational age methods. The PI yields an index to indicate if an infant is underweight for its length (weight in grams times 100 devided by the cube of body length in centimeters). Low PI newborns are typically less than or equal to the third or fifth percentile on a scale plotting PI as related to gestational age. High PI infants are greater than or equal to the 95th or 97th percentile. For example, a weight-length ratio of less than 2.17 for the 37 week gestation infant and 2.20 for the baby with 38 or more weeks gestation has been used in the diagnosis of fetal malnutrition. Unlike weight for gestational age norms, this index of fetal malnutrition is relatively independent of sex, race, and parity of the newborn and the physical size of the mother. Infants with low PI's have little or no subcutaneous fat and visually appear malnourished. Some infants who were diagnosed as sga according to birth weight by gestational age (less than the third percentile) were considered well grown because their PI's were well above the

third percentile and their crown-heel lengths were normal (Miller & Hassanein, 1971).

Crane and Kopta (1980) describe two types of IUGR, symmetric and asymmetric. The former refers to the subsequent and proportionate reduction in size of all body organs whereas the latter affects some body organs more than others. Etiology is distinct for these two types of growth retardation. Factors responsible for symmetric growth retardation include intrauterine infections (e.g. TORCH agents), chromosome abnormalities, congenital anomalies, maternal malnutrition, and smoking. Ultrasonically, the symmetric sga fetus demonstrates a proportionally reduced growth potential prior to the third trimester. Etiologic factors in asymmetric IUGR include uteroplacental insufficiency and is commonly seen in pregnancies complicated by chronic hypertension, pre-eclampsia, and advanced diabetes. Ultrasonically, growth is essentially normal until some point in the third trimester following which fetal head growth is relatively spared but other structures evidence reduced growth (Norman, 1982). Differential diagnosis is made ultrasonically and/or in light of the existence of factors which predispose to one of the forms of IUGR. All 33 infants in the Crane and Kopta study (1980) plotted below the tenth percentile for gestational age, however, only 50% of the asymmetrically growth retarded infants had low PI's and 54% of the symmetrically growth retarded had low PI's (less than the tenth percentile for gestational age), thus indicating that the IUGR sample may vary considerably according to the use of a particular diagnostic classification system.

Jones and Roberton (1984) do well to point out that there exists a group of infants who show symmetrical reduction in size at birth, but who are small for genetic reasons. Ethnicity, maternal size, and socio-economic factors influence the size of some of these small but normal babies.

It seems clear that the absence of uniformity in methods for determining which infants are sga can produce a heterogenous group of growth retarded infants. This has implications for the next section which surveys prognosis. Specifically, it suggests the liklihood that different classification methods will select out different subgroups of sga children, thus raising the possibility of differential outcomes. Accordingly, the ensuing review will be organized by method of classification. Birth weight by gestational age studies will be reviewed first, followed by studies employing the PI, and lastly, those making reference to the timing of onset of fetal growth retardation.

Prognosis for Small for Gestational Age Infants

A wealth of material exists regarding outcome for infants labeled sga. It will be the purpose of this secion to review the findings and to draw some conclusions regarding this heterogenous group of children. Before the review commences, it seems noteworthy to point out that medical management of newborns has changed drastically in the past 30 years. Thus, the deleterious outcomes so long associated with infants of low birth weight (weight less than five and one half pounds at birth), of whom some are sga, may have been due in part to such former neonatal practices as prolonged fasting and administration of lethal and sublethal concentrations of

oxygen to the immature neonate. Thus, a more optimistic outlook in recent studies might be expected to reflect recently improved standards of care (Hack & Fanaroff, 1984; Nelson & Ellenberg, 1984; Sokol, 1984).

Birth Weight by Gestational Age

By far the majority of studies have classified the fetally malnourished infant according to various weight by gestational age curves. The most frequently used criterion for determining the sga infant is less than or equal to the tenth percentile. Note will be made in the ensuing studies wherever this standard is deviated from. Within this method of classification, we will examine in sequence, physical, neurological, intellectual and academic, and psycho/social growth patterns. These distinctions are somewhat arbitrary and will overlap to a certain extent, yet nonetheless seem necessary in order to assimilate the studies to follow.

Physical Growth. In a study investigating the later growth patterns of sfd infants (eliminating cases complicated by prematurity, defined as gestation less than 37 completed weeks; multiple gestation; chromosomal defects and congenital anomalies; and using a criteria of two standard deviations below the mean for weight by gestational age), Fitzhardinge and Steven (1972) found most aspects of growth still retarded at four to six years. Later growth could not be predicted by the degree of weight retardation at birth, but was found to relate instead to the rate of growth in the first six months. Of those sfd infants attaining normal height, a significantly greater than normal growth velocity was noted to occur during the first year. Among the sfd children who remained shorter

than normal, a higher proportion were in the lower income group, thus implicating poor home environment as affecting growth. Assessment of these same children in adolescence while controling for SES and maternal size (excluding those who had moderate or severe asphyxia as defined by five minute Apgar scores and/or occurrence of first breath) revealed significant deficits in height, weight, and head circumference at 13 to 19 years of age (Westwood, Kramer, Munz, Lovett & Watters, 1983). Similar results were obtained in the studies by Low, Galbraith, Muir, Killen, Karchmar and Campbell (1978) and Low, Galbraith, Muir, Killen, Pater, and Karchmar (1982). They noted small but significant differences in the growth measures between the mature IUGR and matched control children from birth to 60 months. Additionally, the IUGR group demonstrated accelerated growth during the three months after delivery, but this failed to result in catch up effects in later childhood. An increased prevalence of maternal smoking and a lower male-female sex ratio of children were noted in the IUGR group; either of which may have functioned so as to lower mean growth scores. Neligan, Kolvin, Scott and Garside (1976) investigated growth parameters of four groups of children; normal controls, premature, sfd, and vsfd (very small for dates which were less than the fifth percentile) children and found that the vsfd group measured consistently and significantly shorter and lighter than the premature children up to seven and a half years of age. The sample subjects had a history of known growth retarding perinatal factors. Social class was not associated with increased growth in the sfd group. Kumar, Anday, Sacks, Ting and Delivoria-Papadopoulos (1980)

examined preterm and fullterm lbw infants. Infants who were appropriately grown for their gestational age (aga) and sga infants (greater than two standard deviations and less than two standard deviations respectively) who had various perinatal risk factors and neonatal complications were included. At one year of age, weight less than the third percentile occurred in eight percent of the aga group and in 46% of the sga group. Height less than the third percentile occurred in 13.5% and 38% of the aga and sga infants respectively. None of the sga infants had heights or weights greater than the 50th percentile at one year. These findings compare to the results of Commey and Fitzhardinge (1979) who assessed preterm sga (less than two standard deviations) infants (excluding congenital and chromosomal anomalies) during the first two years of life. Most children continued to show growth retardation. Thirty four percent had heights and weights below the third percentile at two years of age. Accelerated growth velocity beginning at or slightly before the term date and for six months thereafter was noted. However, because of the early postnatal delay in growth, the cumulative linear growth from birth to six months postterm was virtually identical to the standard for normal term infants.

Evidence for prolonged growth deficits despite accelerations in growth velocity in the first year of life are reflected in other studies. In their study of preterm sga (less than two standard deviations) and aga infants, Hack and Fanaroff (1984) found catch up growth through eight months in both groups. Some of the aga infants continued to catch up during the second year. By the third year,

46% of the sga and 17% of the aga infants continued to be subnormal in weight. Fewer sga infants with subnormal intrauterine head growth caught up in weight by age three than those with normal intrauterine head growth. This seems to suggest that poor catch up growth occurs in sga infants who suffered from early, prolonged, and severe intrauterine growth failure. The studies of Vohr, Oh, Rosenfield, Cowett and Berstein (1979) and Vohr and Oh (1983) followed a sample of preterm sga and aga infants over a five year period. Excluded from the study were children with congenital anomalies and genetic defects. Catch up effects were noted, resulting in comparable weight and height measurements between the two groups at one year. At two through five years, aga infants were significantly heavier. Significantly greater height was noted at two, three, and five years in the aga group. SES was significantly correlated to outcome. Similarly, Tudehope, Burns, O'Callaghan, Mohay and Silcock (1983) note comparable physical growth parameters on their 12 month old preterm vlbw (very low birth weight) aga and sga children. However, both groups continued to evidence subnormal growth at this corrected age, with 20% of aga and 30% of sga children with weights still less than two standard deviations below the mean. This difference was not significant and did not predict later developmental outcome. In their study of Indian preterm aga and sga children, Bhargava, Kumari and Choudhury (1984) note catch up effects in the aga group at three to four years, so that at five to six years, this group was comparable to normal children on measures of height and weight. In contrast the sga group showed no catch up effects from birth to six years of age.

Neurological Growth. Several studies have examined the incidence of neurological sequelae in sga infants. One of the problems of these studies is that oftentimes the neurological measures are poorly identified in the study or not identified at all, making comparison of findings rather difficult. Neurological measures can include hard and/or soft signs, encompassing seizures, cerebral palsy, speech defects, hyperactivity, learning difficulties, etc.

Fitzhardinge and Steven (1972) followed mature sfd infants over a minimum of five years on a variety of measures and compared the results to a sibling group. The sfd group had more speech defects and a higher incidence of minimal brain dysfunction, characterized by hyperactivity, short attention span, learning difficulties, poor fine coordination, and hyper-reflexia than did the control group. No differences in hearing or vision were observed between groups. Some form of speech abberation was noted in 33% of the sfd boys and 26% of the sfd girls. Neligan et al. (1976) similarly found significantly increased incidences of both soft and hard neurological deficits in vsfd infants as compared to normal controls or children with a shorter gestation at six and seven years. Moreover, this was significant for boys and not for girls, suggesting a greater vulnerability for boys. Social class was related to neurological abnormality for both soft and hard signs for the sfd (including vsfd) and control groups. Additionally, language skills were significantly poorer at five years of age in the sfd and vsfd groups compared to controls, and at seven years between the vsfd group and the control group.

Rubin, Rosenblatt and Balow (1973) found significantly higher incidences of neurological abnormalities for both their preterm and mature lbw groups as compared to their higher birth weight preterm and term infants during the neonatal period, at 12 months, and at seven years. The fullterm, lbw infants correspond to a criterion of sga infants less than the tenth percentile. The preterm lbw group is most probably comprised of a heterogenous group of sga and aga infants; though the authors are rather vague on this. At four months the preterm lbw group had the most neurological abnormalities (as assessed by 73-123 items administered by a physician specially trained in pediatrics or neurology). Additionally, motor development at eight months and language skills at five years were inferior in both lbw groups. Overall, the premature lbw group tended to score worse than the mature lbw (sga) group.

Drillien (1970) found an increased incidence of major and minor congenital anomalies and neurological defects (defined as presence of cerebral palsy, epilepsy, or both) in the sfd group compared to other lbw groups. The total incidence of all congenital anomalies was 47% in the sfd group (less than the tenth percentile) compared to 36% and 25% respectively in the ten to 25 percentile group and the group of infants with weights greater than the 25th percentile. In a later study (1972) the author found a higher incidence of transient abnormal neurologic signs suggestive of cerebral palsy during infancy but who were neurologically normal at one year among the sfd group. Of those infants showing these transient signs, there were increased incidences of mental retardation or borderline retardation by two to three years of age.

In considering Drillien's findings, it is important to note that these sfd infants were heterogenous in regards to gestational age, thus blurring the distinction between outcomes for premature and term fetally malnourished infants and later sequelae.

Commey and Fitzhardinge (1979) similarly found an increased incidence of neurological handicaps in their sga group. Twenty one percent had major neurological defects (e.g. hydrocephaly, cerebral palsy, recurrent nonfebrile seizures) and 42% had Bayley scores less than or equal to 80. These children were premature and evidenced a variety of pregnancy and neonatal complications. Presence of cerebral depression upon admission to the Neonatal Intensive Care Unit was significantly associated with later handicap. Birth asphyxia was an earlier complication in 21 of the 24 surviving infants admitted with cerebral depression, 15 of whom were later handicapped. No relationship was shown between neurological sequelae and SES, degree of IUGR, or degree of prematurity.

Incidence of neurological defects have been further investigated by Ellenberg and Nelson (1979). These authors found that mature sfd infants composed a small nonsignificant subgroup who later had cerebral palsy or seizure disorders. In the case of the former, lbw and short gestation were more important risk factors. Similarly, Collins and Turner (1971) found a subgroup of sfd term infants in the patient records of aproximately 14% of their mentally retarded sample. IUGR comprised the second highest risk category in a study by Fitzhardinge, Kalman, Ashby and Pape (1978) investigating handicapping defects. Fifty three percent (21/40) of the sga children had major handicaps at two years of age (defined as the

presence of a major neurological defect such as epilepsy, cerebral palsy, or hydrocephalus and/or a mean Bayley score of less than 80), four presented with neurological defects only, seven with neurological defects and low Bayley scores, and ten with low Bayley scores in the absence of major neurological defects. In order to assess the effects of IUGR apart from premature birth and subsequent postnatal complications, the sga infants were paired with an aga infant of the same birth weight and sex and a similar neonatal course. The sga infants had significantly more major neurological defects and lower Bayley scores than the aga infants, thus implicating poor fetal growth in poorer prognosis.

In their study of lbw infants in India, Bhargava et al. (1984) note that developmental lags in motor and language skills were apparent in the extreme lbw (less than 1500 grams) and sga infants compared to preterm aga and normal babies. In particular, the sga group manifested developmental arrest in the acquisition of the skill of abstraction. This became more pronounced with age. Unfortunately, neither measures, methods, nor statistical findings were reported in the study.

Kitchen, Ford, Orgill, Rickards, Astbury, Lissenden, Bajuk, Yu, Drew and Campbell (1984) in their study of very lbw infants (500 to 999 grams) found a 30% (three of ten) incidence of severe functional handicap in their two year old sga children. Severe functional handicap was considered present in children who had one or more of the following: moderate or severe cerebral palsy, a Bayley Mental Developmental Index less than 69 (less than two standard deviations below the mean), sensorineural deafness

requiring the use of hearing aids or bilateral blindness. No statistically significant differences in social or perinatal variables were noted between the aga, sga or multiple birth groups.

Several studies have examined the motor development of sga infants in an attempt to determine the incidence of neurological defect. Michaelis, Schulte and Nolte (1970) examined mature sfd infants presenting various birth and pregnancy complications (e.g. multiple gestation, forceps delivery) during the first week of life. They found significantly more abnormalities suggestive of greater neurological immaturity in this group as compared to a mature aga group of infants. However, at nine months of age, the sfd group had normal developmental quotients on the Gesell, suggesting that the previously noted immaturity is not persistent in its effects (Parmelee & Schulte, 1970). Similarly, Paine and Pasquali (1982) found no evidence of neurological impairment as assessed by motor development in their group of Brazilian term sfd infants at four, eight, twelve and eighteen months. They excluded from their sample conditions known to be associated with poor intrauterine growth (e.g. congenital anomalies, chromosomal abnormalities, prenatal infection, maternal chronic disease). At 18 months, lower SES and increasing maternal parity were the most important sources of variation in explaining lower psychomotor scores.

Several studies reflect this more optimistic note regarding neurological sequelae. Tudehope et al. (1983) found nonsignificant differences on neurological and sensory handicap status between their premature vlbw aga and sga children. In their study of preterm sga and aga infants, Hack and Fanaroff (1984) note a greater

incidence of neurological sequelae in the aga group, including increased rates of transient hypotonia, cerebral palsy, hydrocephalus and blindness. This was felt to be attributable to the shorter mean gestation for the aga group compared to the sga group. Vohr and Oh (1983) note comparable rates of major neurologic abnormalities (seizures, spastic diplegia, hemiplegia) between their groups of five year olds who were preterm aga and sga at birth. However, a 26% incidence of minor neurologic abnormalities (language delay, fine motor inefficiency and attention deficit) were noted in the sga group compared to 12% in the aga group. SES was significantly correlated to developmental outcome. Developmental test scores were significantly lower for the sga group from nine months to three years. At five years of age, the two groups were comparable, suggesting the importance of following these children over time. Parmelee and Schulte (1970) examined term sfd children with various known growth retarding factors and found they performed similarly to the normal controls at nine months of age. They also compared favorably regarding neurological maturity as determined by nerve conduction velocities to the normal control group. The Low et al. study (1982) of term IUGR children from one to six years of age similarly included various known factors affecting fetal growth. Despite this, no significant differences on motor or language development, or in visual or hearing defects were noted in the IUGR group compared to the aga control group. However, the IUGR group had a higher proportion of motor and language handicaps. Slightly elevated WPPSI full scale scores at 60 months were noted for males in the IUGR group compared to the male controls (106 and 103

respectively). The Westwood et al. study (1983) found no major organic neurologic signs in the nonasphyxiated subgroup of sga infants in adolescence. Similarly Vohr et al. (1979) found comparable outcomes at one year with sga and aga children. At 18 months, the sga group had lower Bayley scores but this difference was not present at 24 months.

The more favorable findings in these last few studies may reflect in part different birth cohorts and changes in neonatal care in more recent years. Another possible explanation is that it may reflect the less stringent criterion of defining the sga samples as less than or equal to the tenth percentile on growth curves or to the exclusion of certain subgroups of sga infants, as in the Westwood et al. study (1983). In other words, the inclusion of more adequately grown healthy infants may have the effect of raising the mean group scores on various outcome measures.

Intellectual and Academic Growth. A pattern of normal IQ scores but academic problems are suggested by various studies of sga children. Hack and Fanaroff (1984) note nonsignificant differences between their preterm sga and aga children. IQ scores on the Stanford Binet at three years were slightly lower for the sga group, but mean scores were still in the normal range. Babson and Kangas (1969) note IQ scores in the normal range at four years of age for their term sfd group and a nonsignificant three point difference with the control group. Fitzhardinge and Steven (1972) similarly note normal IQ scores in their mature sfd group at four, six, and eight years of age, with boys scores averaging six points less than the girls scores (95 compared to 101). However, a high incidence of

school failure was reported in the sfd group, with 50% of boys and 36% of girls functioning poorly in school. Seven of the 16 unsatisfactory scholars had been assigned to either a special school or a special class. The remainder were consistently failing subjects in the regular classroom. Evidence of academic problems were not apparent in the sibling control group. No relation between degree of poor fetal growth and either intelligence or school performance were noted. Normal IQ scores were again noted in the Rubin et al. study (1973), however significant differences were found in the two lbw groups (a preterm and a fullterm group) compared to the higher birth weight groups. The proportion of retentions, special class placements and use of special services were more prevalent in the two lbw groups, with more special educational problems being noted in the term lbw group (or sfd) than in the preterm lbw group. A 50% incidence of special educational problems were noted in the sfd group. Two thirds of boys in both lbw groups accounted for a higher proportion of school identified educational problems than did the girls of similar birth weight. Francis-Williams and Davies (1974) note the same pattern of normal IQ scores which were significantly lower for the preterm sfd group compared to the aga group. This group of sfd children had various pre- and perinatal complications and were over represented in the lower classes, thus confounding these findings. Neligan et al. (1976) found normal IQ scores at five years of age for sfd and vsfd groups, however these scores were significantly lower than those for normal controls. A battery of cognitive and sensory motor functions were administered at five to seven years of age with the general

finding that the vsfd group most often performed the least maturely of all the groups. However, sex and social class were significantly associated with outcome.

More recently, Drillien. Thomson, and Burgoyne (1980) investigated sequelae of sfd infants with variable term status at six years of age. They found that the presence of transient abnormal neurological signs in the first year of life was predictive of schooling problems in the sfd and lbw groups. This finding may be due to an increased incidence of postnatal complications as compared to the neurologically normal infants in the first year. Intelligence scores were normal but slightly lower in the sfd group. Correlated to low scores on measures of intelligence and educational achievement were low social class, male sex and early intrauterine insult. Cases with known growth retarding factors were not excluded from this study. This is similar to the nonsignificant differences on multiple measures of cognitive development at two to five years of age which were noted in the Low et al. study (1982). In this study, more sfd children failed senior kindergarten (15% compared to seven percent in the aga group), however the difference was not significant. Socio-economic status correlated to outcome in this study. Tudehope et al. (1983) note lower, but nonsignificant differences between their groups of preterm sga and aga children at three to four years of age on the McCarthy Scales of Children's Abilities.

Westwood et al. (1983) further elucidate these findings in their assessment of adolescents who were unasphyxiated sga newborns. They found nonsignificant trends towards lower scores on the WAIS

and WISC when compared to the normal birth weight control group, while controlling for SES and maternal size. However, most scores in both groups were well in the normal range. In an attempt to reconcile these relatively mild findings with the severe cognitive deficits reported by Fitzhardinge and Steven (1972) on the same subjects at a younger age, the authors compared the 11 excluded asphyxiated sga infants to the nonasphyxiated sga infants. The mean full-scale IQ was 87.1 in the asphyxiated subgroup compared to 101.1 in the nonasphyxiated subgroup. Thus, the poorer outcomes for sga children may result from perinatal asphyxia or other complications in the neonatal period, rather than from IUGR.

Psycho/Social Growth. One might expect to find an increased incidence of psycho/social problems (either at home or at school) in children evidencing significantly more school related problems. However, the studies cited regarding school problems failed to investigate what may be concomitant problems to academic difficulty. The Neligan et al. study (1976) however, does examine psycho/social sequelae at five to seven years of age. In the area of behavior, significantly more abnormalities were noted in the vsfd group as compared to the premature group according to mother, teacher, psychologist, and psychiatrist reports. Boys in both groups were significantly more likely to exhibit behavioral abnormalities than were girls. Additionally, social class particularly in the sfd group, was related to behavioral abnormality. A hyperactive pattern was especially pronounced in the sfd group. This resembles the higher incidence of hyperactive behaviors found in the Fitzhardinge and Steven study (1972). Measures of temperament showed few

differences at age five between groups, however of the eight items that were worse for the vsfd children, five were related to a pattern of high activity. This pattern of high activity continued to be apparent at seven years in both the vsfd and short gestation groups. Personality scores at seven years of age on an extraversion and neuroticism indice revealed nonsignificant differences between groups (Neligan et al. 1976). Bhargava et al. (1984) note poorer outcome in adaptive and personal social skills in their sga group of Indian children. However, as noted previously, measures, methods, and statistical analyses are not reported.

Summary. In studies which have examined sga children using a criterion of various growth curves, evidence indicates a normal pattern of physical maturation. However the children remain consistently shorter and lighter throughout childhood and adolescence, particularly in studies using stricter criteria for sample selection or those excluding certain unhealthy subgroups of sga infants. (An exception to this may be a subgroup of preterm sga infants whose early delivery facilitates normal growth and prevents sequelae associated with fullterm pregnancy complications.) Normal intelligence is consistently found, but higher rates of neurological abnormalities, including motor, speech and language delays, presence of cerebral palsy, epilepsy, mental retardation, sensory loss, hyperactivity, and academic problems have been reported in several studies, although the differences are not always significant. The majority of studies contained subjects with known growth retarding factors (e.g. maternal chronic disease, multiple gestation, etc.) and various neonatal complications including asphyxia and/or preterm

status which may tend to obscure the findings. It may well be that certain subgroups of sga children do have an increased incidence of neurological defects and academic difficulties which tend to elevate the mean incidence of problems for the sga group as a whole (Ounsted, 1970). Sex and social class tend to be the most frequently cited covariates to outcome in the studies reviewed thus far, with parity and neonatal complications being implicated as well. Those children with the best overall prognosis tend to be mature female children of higher SES with an absence of known growth retarding factors in their pre- or perinatal history. There is some evidence to suggest that more recent birth cohorts may fare better too; but this is not consistent.

The preceding discussion suggests a number of significant factors to measure in this study. Presence of IUGR will be important to note since this correlates to later neurological, academic and behavioral difficulties. This leads us to expect poorer outcomes for children with HEV affected placentas due to the increased rate of IUGR in this group. Male sex and increased parity are also considered to be risk factors in some of the studies reviewed and so will be of concern to us here. Various complications of birth, such as cesarean delivery, fetal distress, lbw, and length of gestation are also linked in the literature to poorer outcome and will therefore be examined here. Additionally, SES has correlated to prognosis, therefore various components of SES will be measured in the study at hand, including parental education, income level, marital status, and maternal age at time of delivery.

The Ponderal Index (PI)

It has previously been pointed out that the various classification systems are not mutually exclusive, nor reliable in selecting sga subjects. For example, fetal growth retardation in low PI infants is noted to begin a few weeks before birth, thus overlapping with the asymmetric form of fetal growth retardation to be discussed in the next section (Walther & Ramaekers, 1982a, 1982b; Zeskind & Ramey, 1978). In spite of this, the ensuing discussion will look towards the expanding knowledge base regarding sequelae for sga children as contributed to by this method.

Physical Growth. Healthy mature infants were examined in a study by Davies, Platts, Pritchard and Wilkinson (1979) which compared disproportionally grown sga infants (less than the third percentile) to proportionally grown sga infants (greater than the tenth and less than the 50th percentile). They found the disproportionately grown (or late onset of IUGR) infants grew more rapidly during the first month than did the proportionately grown (or early onset) infants. Thereafter, growth rates were similar. Both groups had greater growth velocities in the first three months after birth than did normal term infants. This period of catch up effects was also noted in the Walther and Ramaekers study (1982a) which assessed healthy term sga and aga children. The sga group evidenced a greater growth velocity than the controls during the first six months. Despite the above average rate of growth, 13 out of 25 sga infants (compared to two out of 25 controls) had weights below the tenth percentile at three years of age and nine (compared to three controls) were below the tenth percentile for length.

Neurological Growth. Walther and Ramaekers (1982b) note that language development is dependent on the biological maturation of the brain, and as such is useful in assessing higher cerebral function in preschool children. Thus, term sfd infants (who were free from fetal disease and neonatal morbidity) and matched normally grown controls were assessed at the age of three years on the Reynell Developmental Language Scales. The mean raw scores and corresponding mean developmental ages were worse for the sfd children than for the controls. The differences were significant and amounted to four months for verbal comprehension and five months for expressive language. Language retardation (scores less than or equal to two standard deviations below the mean) was observed in eight percent of the controls compared to 32% of the sfd group. Additionally, the incidence of behavior problems in language delayed sfd children was high as was neurological dysfunction in sfd children with either delayed or adequate language. These findings compare to the results in the Fitzhardinge and Steven study (1972) previously reviewed who used a different measure of IUGR but found an elevated incidence of speech problems and minimal brain dysfunction in their three and four year old subjects.

Zeskind and Ramey (1978) investigated motor development in low PI and normal PI infants. Fullterm full birth weight black infants from low SES families, with no serious prenatal or perinatal complications were studied. They were assigned to either an instructional day care program or to a nonintervention control group. At three months of age, both low PI groups (i.e. the day care program and control conditions) showed significantly lower

motor development scores than the normal PI group. A significant difference between scores in low PI and normal PI infants in the home control group was still present at 18 months, however the difference between low and normal PI infants in the day care program had disappeared. Additionally, normal PI infants in the day care program had higher motor development scores than normal PI infants in the control group at 18 months of age. Thus the differences that characterized the fetally malnourished group at three months were ameliorated in the supportive day care environment. In another study examining motor development during the first year of life, Goggin, Holmes, Hassanein and Lansky (1978) found no significant differences between healthy fullterm low, normal, and high PI infants. However, this study used subjects with diverse socio-economic status which may account for discrepant findings from the Zeskind and Ramey study.

The newborn period has been the subject of investigation in several studies examining neurological sequelae in low PI infants. For example, Zeskind and Ramey (1981) analyzed the cry features of low, normal, and high PI fullterm full birth weight infants who were without evidence of pre- or perinatal complications. They found that infants at both extremes of the PI were characterized by cry features which have been shown to distinguish infants whose central nervous system functioning has been impaired (e.g. threshold, latency, activity, and fundamental frequency of cry). Als, Tronick, Adamson and Brazelton (1976) examined caucasian healthy term infants on the Brazelton Neonatal Behavioral Assessment Scale during the first ten days after birth and found significant differences between

the low and normal PI groups on motor behavior and interactive processes. Organization of state and physiological stability were comparable between groups. All newborns were informally assessed later prior to nine months on the Denver Developmental Screening Test and were found to perform within normal limits, thus offering similar results to the Goggin et al. study (1978).

Intellectual Growth. The Zeskind and Ramey studies (1978, 1981) investigated cognitive development in inadequately grown children. They found at 18 and 24 month assessments, no significant differences between low and normal PI children in the day care setting. However, low PI children showed significantly lower scores at 36 months than did normal PI children within the control environment. Thus the detrimental effects of fetal malnutrition in lower class black children were observed at three years in an intellectually nonsupportive environment, but were ameliorated with the provision of an intellectually supportive atmosphere.

Psycho/Social Growth. Several studies have investigated different aspects of the parent-child relationship in low PI children. Receiving particular research focus have been various interactional variables, of which the investigations of Zeskind and Ramey have made especially noteworthy contributions (1978, 1981). The authors implicate the simultaneous action of various agents, which taken together have a total effect that is greater than the sum of the parts. For example, it is argued that the removal of one factor in the fetally malnourished infant's environment may prevent part of the cyclical occurrence of nonoptimal development. This can be seen in the parent-child relationship that develops with the low

PI infant who had qualitatively distinct cry features in infancy. At 18 and 30 months of age, mothers of low PI infants in the nonintervention group were significantly less involved with their children than mothers in any other group. The low PI infants in the nonsupportive environment also showed poor intellectual development and fewer positive social behaviors than other groups. Thus it is posited that the malnourished infant may put off the caregiver in a nonsupportive environment in which the infant behaviors persist, thus exacerbating a cycle of nonsupportive infant and maternal interactive behaviors. However, in a supportive environment this cycle is not established. Instead, the low PI child develops normally as a function of the supportive day care environment, which effects the quality of the infant-maternal pattern of interaction. This transactional process is further elucidated by the Als et al. study (1976) wherein the low PI infants were significantly less responsive to social stimuli and deficient in interaction processes at ten days. Additionally, eight of ten mothers reported problems of temperament, rhythmicity, and activity level at one and a half to nine months of age. The Goggin et al. study (1978) found a significant increase of maternal negative feedback in social interactions with their infants in the low PI group during the first year of life. Thus, distinctive cry patterns, social unresponsiveness and deficient interactional processes in infancy appear as part of the cycle that eventuates in decreased maternal involvement, increased maternal negative feedback and decreased positive social behaviors by the child at three years of age.

Summary. Studies utilizing the PI as a means of classifying the fetally malnourished infant have tended to concur with and substantiate results arrived at using weight by gestational age growth curves. Deficient growth, and speech and behavior problems were again noted in the IUGR group. However, findings of abnormal neurological and cognitive development may relate more to the nonsupportive nature of the caretaking environment, particularly for healthy sga infants in lower SES groups, than to the status of being fetally malnourished; a finding not readily apparent in the birth weight by gestational age criterion studies. Additionally, parent-child interaction variables and social development may be transactionally related.

Findings in this section of our review point to the importance of assessing the home environment and aspects of the parent-child relationship in order to understand sequelae for our target group of children. Use of the Family Relations scale on the Personality Inventory for Children-Revised (PIC-R), Dimensions of Temperament Survey-Revised (DOTS-R), and maternal interviews will yield information in these important areas.

Timing of Onset of Fetal Growth Retardation

The distinction has previously been made between the onset of IUGR and its associated maternal, placental, and fetal factors (Crane & Kopta, 1980). Diagnosis of onset of IUGR in the majority of studies reviewed here was by serial ultrasonic cephalometry. Slow intrauterine growth was defined as a weekly measurement of biparietal diameter (reflecting head and brain size) which is below the fifth centile for a period of two weeks or more. The time of

onset of growth failure was determined on the graph of the normal range by establishing the point at which the fetal growth line deviated from normal. When slow growth was of short duration, the onset was usually clearly defined. In cases of prolonged growth failure, slowing often occurred prior to the first ultrasonic measurement. This method was used in all but the Winer, Tejani, Atluru, DiGiuseppe and Borofsky study (1982). The method used by Winer et al. (1982) to determine the timing of onset of IUGR will be noted in the ensuing discussion.

Physical Growth. Fancourt, Campbell, Harvey and Norman (1976) used a criterion of birth weight by gestational age (less than the tenth percentile) to select their four groups of term sga subjects. The groups were as follows: 1) growth failure less than or equal to 26 weeks; 2) greater than 26 but less than or equal to 34 weeks; 3) greater than 34 weeks; and 4) no evidence of growth failure. Excluded were children with known growth retarding factors associated with onset prior to the third trimester, thus there was an over preponderance of asymmetric growth retardation (onset in the third trimester) in this sample. They found that children whose head growth began to slow in utero prior to 34 weeks were more likely to have a height and weight less than the tenth centile at four years of age. This was significantly different than children whose growth slowed after 34 weeks or not at all, even when sex and social class were matched. These matched pairs differed significantly on head circumference as well. Winer et al. (1982) examined two groups of four to seven year olds, one group whose mothers had hypertensive disorders during pregnancy and were sfd

(less than the tenth percentile) and another group of sfd children whose mothers had no hypertensive disorder. The former group corresponds to the asymmetric form of late onset growth retardation whereas the latter group corresponds to the early growth failure associated with the symmetric form of growth retardation. Head circumference and weight measures were greater in the hypertensive (late onset) group but this difference did not reach statistical significance, even when SES was corrected. Both groups showed values around the 50th percentile for head circumference, weight, and height.

Neurological Growth. The four growth patterns examined in the Fancourt et al. study (1976) found significant differences when followed up at four years of age on the Griffiths scale which assesses six areas: locomotion, personal-social, hearing and speech, eye and hand coordination, performance, and practical reasoning. Those children whose growth failure began very early (prior to 26 weeks) had a significantly lower mean development quotient than the other three groups. Only the two subscales of performance and hearing and speech failed to reach statistical significance.

Intellectual and Academic Growth. Harvey, Prince, Bunton and Campbell (1976) and Harvey, Prince, Bunton, Parkinson, and Campbell (1982) followed up term sfd children at five years of age with the McCarthy Scales of Children's Abilities. The four groups of differential onset of growth retardation were the same as described in the Fancourt et al. study (1976). Prolonged slow growth in utero (less than or equal to 26 weeks) was significantly associated with lower abilities as assessed by the General Cognitive Index, and four

of the five subscales (perceptual-performance, quantitative, motor, and memory) compared to the other three combined groups. There were no significant differences on verbal scale scores. When the children were grouped by birth-weight percentiles (rather than by timing of IUGR onset), nonsignificant differences were noted on intellectual outcome, suggesting a more deleterious outcome for the subgroup of sfd children suffering prolonged intrauterine growth delay. Parkinson, Wallis and Harvey (1981), using the same four groups plus a matched control group for the two early onset groups, found that children with slowed fetal growth prior to 34 weeks gestation were significantly more likely to have problems in achievement at seven years of age than were children whose growth retardation started later in pregnancy or was not apparent by ultrasonic measurement. Sex and social class were also significantly correlated to outcome. The two early onset groups also had significantly poorer concentration than other groups. Additionally, the very early onset group had significantly lower scores in a variety of subject areas, including reading, writing, and reasoning ability. Sex was again significantly correlated to outcome. These general findings of early growth failure and statistically significant lower scores are further corroborated in the Winer et al. study (1982). The later onset group (with maternal hypertensive disorder) performed better in all phases of intellectual testing than the early onset group, but this reached significance only on the Verbal IQ (on the WPPSI) after SES was corrected. In the late onset group (maternal hypertensive disorders) there was a negative correlation between both birth

weight and gestational age and test scores, indicating that, in mothers who had vascular disease, earlier delivery and the resulting lighter infants did better. It is suggested that this may reflect the late-flattening growth curve pattern, which produces maximum compromise of head growth in late gestation, resulting in a favorable outcome in newborns delivered earlier. In contrast, the early onset group appeared to benefit by prolonged gestation and greater weight at birth.

Psycho/Social Growth. Psycho/social sequelae were investigated in the Parkinson et al. study (1981). The composition of the four groups and a control group have previously been described. No significant differences were noted in the total number of types of atypical behavior among the four sfd groups. However, boys with onset of growth failure prior to 34 weeks gestation had significantly more atypical markings than their normal birthweight controls. These boys were considered by their teachers to be significantly more clumsy, worried, fidgety, unhappy, and upset by new situations. Girls with IUGR onset prior to 34 weeks evidenced significantly more crying and irritability than other sfd girls.

Summary. The reviewed studies suggest that early onset of growth failure is more frequently associated with poorer physical growth, and more immature neurological, intellectual, academic and psycho/social functioning than is late onset of IUGR. However, the Winer et al. study (1982) suggests that shorter gestation in the presence of maternal hypertensive disease (IUGR of late onset) is correlated to improved cognitive outcome. Sex and SES variables continue to be associated with prognosis.

These readings raise implications that have an impact on the current study. First, we might expect poorer outcomes where the pregnancy history is suggestive of early growth failure. Second, shorter gestations and lighter weights may be associated with better outcomes where maternal hypertensive disorders have complicated the pregnancy and birth.

A Review and Synthesis

Several areas having implications for a follow up study of children with HEV affected placentas have been reviewed. The chapter began with a brief survey of the placenta as a biopsy specimen for determining pathology, particularly regarding its usefulness in assessing the presence of viral infections. A discussion of chronic villitis and villitis of unknown etiology followed, noting than an infectious origin is documented in the former case and suspected in the latter. (Eleven percent of HEV affected placentas between 1978 and 1980 suggest the possibility of some type of viral infection, although this isn't conclusive at this time.) Sixty percent of the placentas evidenced chronic villitis. Additionally, VUE and TORCH agents by implication are associated with an increased incidence and severity of intrauterine growth retardation. A brief review of sequelae of congenital CMV infection (an etiologic agent in chronic villitis and a small percentage of HEV affected placentas) indicated significantly higher incidences of neurological handicap in these children.

Fetal growth retardation is associated with 33% of HEV affected placentas. A review of outcome studies indicates that sga children are a heterogenous group. It is possible that certain subgroups

have more deleterious outcomes than others. Boys, lower socio-economic classes, infants with neonatal complications, samples using more stringent criterion for defining sga (e.g. less than the third percentile), increased parity, or prolonged intrauterine growth retardation and/or associated factors (e.g. TORCH infections, congenital abnormalities, chromosomal anomalies, smoking, etc.) may be among those subgroups of sga children appearing to be at greater risk for later sequelae. Additionally, prolonged gestation with maternal hypertensive disease may be likely to result in poorer prognosis at follow up. Despite these many risk factors, there continues to be evidence suggesting the mediating influence of a more optimal environment on prognosis.

Thus, a variety of factors will be important to make note of in the ensuing study. In particular, documentation of TORCH or other viral agents, chronic villitis, fetal growth retardation, maternal and fetal factors associated with IUGR, sex, and socio-economic variables. It will be critical to the purpose of this study to determine which of the preceeding factors may be associated with later sequelae in children with HEV affected placentas.

Hypotheses

The present study assessed children in three groups: those with HEV affected placentas, a Registry control group, and a community control group. Outcome measures include the McCarthy Scales of Children's Abilities (MSCA), Personality Inventory for Children-Revised (PIC-R), Dimensions of Temperament Survey-Revised (DOTS-R), Bender Gestalt (BG), and presence or degree of handicapping conditions.

The following hypotheses were generated:

1. Those children with HEV affected placentas will do the poorest on outcome measures. The Registry control group will have lower scores than those children in the community control group but not as low as the children in the HEV group.

2. Male sex will be associated with poorer outcome.

3. Certain factors in the pre-, peri-, and/or postnatal environments will correlate to poorer prognosis. These factors include the presence of chronic maternal disease, multiple gestation, fetal distress, increased parity and gravida, cesarean section, maternal hypertensive disease, pre-eclampsia smoking in pregnancy, abnormal Apgar scores, male sex, low birth weight, earlier gestation, increased maternal age, greater ordinal position, minority group membership, and disrupted marital status (e.g. single, seperated, or divorced).

4. Socio-economic variables will be positively correlated to outcome. Parental education level and income at time of birth and time of assessment will be examined.

5. Presence of fetal growth retardation will be associated with lower scores. Additionally, early onset of delayed fetal growth will correlate to poorer outcome than will late onset of fetal

growth retardation.

6. Presence of congenital viral infection will be associated with poorer prognosis.

CHAPTER III

Methodology

This chapter outlines the methodology employed in the study. Discussion will focus on the design of the research, including a description of the pilot study, sample selection, contact procedures, instrumentation, and methods for analysis.

All procedures described were conducted either by the author (LE) or the field epidemiologist (LK). The former was responsible for child assessments, while the latter was in charge of securing subject participation, doing maternal interviews, and abstracting data from medical records. This arrangement allowed the author and study participants to be blind to group status. The field epidemiologist was not blind to group status.

Design

The follow up of children with HEV affected placentas consists of examining the birth records for both mother and infant. Information will be abstracted in a systematic manner regarding health status and medical history. Additionally, those children with HEV affected placentas, born between November 1, 1977 and November 1, 1979, will be assessed at approximately five years of age. Comparison will be made with a Registry control group and a

community control group of children of similar ages. Mothers of all subjects will be interviewed as well.

Description of the Pilot Study

A pilot study assessing 28 children was initiated in 1983; 14 of these children were in the HEV group and 14 were in the Registry control group. Comparison was made with Registry control children, matched on date of birth and location. Assessment consisted of the McCarthy Scales of Children's Abilities (MSCA), the Personality Inventory for Children (PIC), and the Bender Visual Motor Gestalt test. Maternal interviews were conducted simultaneously with the child assessments. A paired t test on the MSCA General Cognitive Index (GCI) found significant group differences ($p < .01$). The GCI significantly correlated with gestational age, birth weight, and ordinal position ($p < .05$) for the HEV group, whereas gestational age ($p < .05$) and maternal education ($p < .01$) correlated with the Registry control group. Additionally, the HEV children exhibited more extreme PIC scores and greater immaturity on the Bender. Differences were not significant on either test.

It was felt that further investigation was needed following the pilot study to see if the differences between groups were maintained and to further clarify the nature of these differences. Thus, the study to be described is a modification and extension of the original pilot study.

Population

Selection Procedures

All 56 cases of HEV associated with live births, referred to the Registry from Michigan's lower peninsula between November 1,

1977 and November 1, 1979 were identified. The objective was to secure 40 participants for this study. Each was matched on location and birthdate to Registry controls having a variety of pregnancy or birth complications, including placental abnormalities, but not HEV. Additionally, a community control group was identified, with the group size of 20 selected. The following selection methods were used.

The log for the Registry was consulted to identify children for the HEV group, excluding stillbirths, neonatal deaths and infancy and childhood deaths. Registry controls were selected by choosing a liveborn infant from the same hospital as each HEV case, while matching as closely as possible on birthdate (with the calendar year plus or minus a month, or a 14 month span, being the parameters). If more than one Registry control was available (as in the instance where a hospital had two infants born on the same day), gestational age was also matched. Where Registry controls were unavailable from the hospital supplying the HEV case (e.g. where a hospital may have sent only one placenta to the Registry during the year and this one had HEV), then a hospital in the same town or a nearby town was used.

In this manner, 40 children with HEV affected placentas were identified. Of the 56 potential cases, 16 were lost to follow up for the following reasons: child deceased-four, moved out of area-four, unable to locate-four, refused-three, child missing-one. Thirty seven Registry control children participated in the study. Of the 48 potential cases, 11 were lost to follow up for the following reasons: moved out of area-seven, unable to locate-one,

refused-three.

The community controls were selected in the following manner. The numbers for each of the 40 children with HEV affected placentas were placed in a hat. Five numbers were randomly drawn. The physicians of these five HEV cases were contacted by letter and then phone, and requested to identify four children by means of their personal delivery log or hospital log; two infants delivered by the physician immediately before and two immediately after the HEV case. These were to be greater than 2500 grams at birth, more than 37 weeks gestation, requiring no special care at the hospital, possessing no congenital anomalies and whose mothers were free of hypertensive disease during the pregnancy. Since none of these children had their placentas examined at the Registry, it is not known if they had HEV.

In this manner, five physicians were located and contacted. One of these was uncooperative. The remaining four doctors supplied names of suitable children; nine of which we were able to locate and secure their participation.

The geographic parameters of the study were identified as being Michigan's lower peninsula or immediately across the Michigan/Ohio border. All participants were born in Michigan hospitals and were assessed at approximately five years of age.

Contact Procedures

The following sequence of events describes the process for locating and contacting all study participants. Initally, letters were sent to the delivering physicians to inform them of the study. Telephone contact with physicians followed, with a request for

assistance in locating the subjects, including information about the child's present physician. Letters and telephone contact was then made to these referred physicians. The procedure was slightly different for the community controls. The physicians were contacted and their assistance sought regarding entering their own hospital or personal delivery log to elicit names for the study subjects. Where hospital logs were consulted, permission to enter these logs was obtained from the hospital. Parents for all three groups were then contacted by letter and telephone to secure their participation. The study was explained in such a way so as to leave the subjects blind to their group status. Letters of informed consent were signed by the parent(s) in each case, with the stipulation that withdrawal from the study at any time was permitted. Testing and interviewing sites and times were established in the subjects home communities. Following the conclusion of the study, provision was made to inform participants as to their group status and general findings upon assessment.

Instruments

The following data collection methods were used: maternal interviews, retrospective examination of hospital records, McCarthy Scales of Children's Abilities (MSCA - a measure of cognitive abilities), Bender Visual Motor Gestalt Test (a measure of visual-motor abilities), Personality Inventory for Children (used in the pilot study) and Personality Inventory for Children-Revised (PIC and PIC-R - a parent-report questionnaire assessing their child's personality), and Dimensions of Temperament Survey-Revised (DOTS-R - a parent-report questionnaire assessing aspects of their child's

temperament).

Procedures

Mothers were interviewed in a private room, all by the same person (LK) who was not blind to their group status. The interview schedule assessed general health, obstetrical history, toxic substance exposure, and health of the child and siblings. Demographic information was also obtained at this time. Mothers were sent the PIC or PIC-R and the DOTS-R prior to the interview, with the instructions to bring the completed forms with them. The PIC and PIC-R yield 12 clinical scales plus an overall adjustment scale: achievement, intellectual screening, development, somatic concern, depression, family relations, delinquency, withdrawal, anxiety, psychosis, hyperactivity and social skills. The DOTS-R includes scales of activity level-general, activity level-sleep, approach-withdrawal, flexibility-rigidity, mood, rhythmicity-sleep, rhythmicity-eating, rhythmicity-daily habits, and task orientation.

Simultaneous to the maternal interviews were the child assessments on the MSCA and the Bender, administered by the author. The MSCA yields scales in five areas: verbal, perceptual-performance, quantitative, memory, and motor skills. A general cognitive index (GCI) is comprised of the first three scales. The Bender was administered to children five years of age or older, using the scoring system devised by Koppitz which yields a developmental score based on number of errors. Both tests are normed at six month intervals. All testing was done by the author using a double blind procedure. Children were assessed in health care or academic settings whenever possible using standardized procedures.

In some instances (approximately ten) the child was tested in their home in a quiet room as free from distractions as possible, when other arrangements could not be made. Children who became anxious during the testing situation were allowed to visit their mothers, following which testing was resumed.

Birth records of mother and child were examined by two individuals, one who was blind to the group status of the participants (a medical student) and one who was not (LK). An abstraction form was devised to elicit and record the information in an objective manner.

Methods of Analysis

Statistical procedures were used to test the research hypotheses. The statistics employed included the ANOVA and chi square procedures, Pearson product and Spearman rho rank correlation coefficients, amd the Bartlett test for homogeneity of variance.

H1 and H2: The chi square and ANOVA statistics were used to determine group differences on the various outcome measures; including the MSCA, PIC-R, DOTS-R, Bender Gestalt, and handicapping conditions. The chi square statistic was used where both variables were discrete, whereas the ANOVA was used when one variable was continuous and one was discrete. A 2 X 3 ANOVA was used to determine group by sex differences on the various outcome measures. Where statistically significant confounding variables were noted to relate to both outcome measures and group status, a multi-factor ANOVA was used to control for the confounding variables.

H3: The Pearson product moment correlation coefficient was used to assess relationships between factors in the pre-, peri-, and postnatal environments and outcome measures: such as chronic maternal disease, multiple gestation, fetal distress, C section, maternal hypertension, pre- eclampsia, marital status, race, sex, smoking and drinking in pregnancy, birth weight, gestational age, maternal age, Apgar scores, chronic villitis, sga, and ordinal position. The Spearman rho rank correlation coefficient was used where group size was very small. In this study, this included analyses for the variables parity and gravida.

H4: The Pearson product moment correlation coefficient was used to test for association of socio-economic variables to later sequelae, examining parental education and income levels at birth and at time of assessment.

H5: The Pearson product moment correlation coefficient was used to assess the degree of relationship between sequelae and sga. Early and late onset of IUGR was analyzed using the Kruskal-Wallis One-Way ANOVA. This nonparametric test is appropriate where group size is small.

H6: The association of congenital viral infection and outcome was assessed by calculating the Pearson product moment correlation coefficient.

Chapter Summary

This chapter has attempted to outline the research methodology. It began with a description of the design, the population, instrumentation, and methods for statistical analysis. In the next chapter, we will view the results of these methods.

CHAPTER IV

Results

This chapter will review the results of the research project following up five year old children with HEV affected placentas. We will begin by describing this target population of children. An analysis of the statistical procedures and findings will follow. Comparison to a Registry control group and a community control group will be made. The analyses to be discussed herein result from the use of the Statistical Package for the Social Sciences.

Description of the Population

This section will delineate the characteristics of five year old children with HEV affected placentas. This data was compiled from maternal interviews and abstractions from birth records. As described in Chapter III, the maternal interviews were conducted in the home communities by LK, the field epidemiologist for the project, who was aware of the participants group status. Birth records were abstracted by LK and a medical student, the latter of which was blind to group status.

Children with HEV affected placentas had a mean age of 63.2 months at time of assessment (range 55 to 74 months). They were born to mothers who were approximately 27 years old at time of this particular birth. Average years of education for mothers was slightly lower than for fathers. However, both parents tended to have graduated from high school (or its equivalent) and to have

received less than one year of school beyond the high school level. Average income level at birth of the child with HEV was in the $15,000 to $20,000 range. By the time of assessment, approximately five years later, the average family was earning in the $20,000 to $25,000 range. Average amount of smoking during pregnancy was less than half a pack a day, with 53% of HEV mothers not smoking at all during this pregnancy. Most of the families were married at the time of assessment. Only 13% were in the category of "not married" (single, divorced, seperated). See Tables 1 and 2 for a summary of these findings.

TABLE 1. Mean Values for Various Continuous Variables by Group Membership

	HEV		Registry		Community	
Variables	mean	n	mean	n	mean	n
Age in Months	63.2	40	64.37	37	67.11	9
Maternal Age	27.15	40	25.32	37	25.0	7
Maternal Education/Yrs.	12.58	40	12.81	37	13.14	7
Paternal Education/Yrs.	12.97	39	12.87	37	13.71	7
Income at Birth*	4.48	40	4.46	37	4.29	7
Present Income*	5.2	40	4.76	37	5.14	7
Gestational Age/Weeks	38.67	39	36.83	36	40	5
Birth Weight/lbs.	5.99	40	6.3	37	7.52	7
Ordinal Position	2.45	40	1.95	37	3.43	7
Smoking in Pregnancy**	.83	40	.78	37	.28	7
Gravida	3.71	38	2.84	37	3.29	7
Apgar: 1 Minute	7.75	20	7.13	16	8.0	3
Apgar: 5 Minutes	9.2	20	8.27	15	9.3	3

*1=0-$5000 2=$5000-$10,000 3=$10,000-$15,000 4=$15,000-$20,000 5=$20,000-$25,000 6=$25,000-$30,000 7=$30,000-$35,000 8=$35,000+

**0=no smoking 1=less than 1/2 pack a day 2= 1/2 to 1 pack a day 3=1 to 1 1/2 packs a day 4, 5, 6, 7= increase by 1/2 pack increments

TABLE 2. Marital Status of Parents by Group Membership*

	HEV		Registry		Community	
	Yes%	No%	Yes%	No%	Yes%	No%
Married	87	13	69	31	71	29

*married at time of assessment

Seventy percent of the children with HEV affected placentas were female. Ninety five percent of the HEV group were white (only two were nonwhite, one black and one hispanic; see Table 3).

TABLE 3. Sex and Race by Group

		HEV	Registry	Community
Sex:	Male%	30	46	56
	Female%	70	54	44
Race:	White%	95	89	100
	Other%	5	11	0

As a group, the children with HEV affected placentas tended to be neither premature nor of low birth weight. Average gestational age was 38.67 weeks (range 29 to 45 weeks) and mean birth weight was just under six pounds (range two lbs. one half oz. to eight lbs. fifteen oz.). These children tended to be second born children in their families, born to a gravida four. Apgars at one and five minutes were normal, with average ratings of 7.75 and 9.20 respectively.

Of particular interest to this study was investigation of pre- and perinatal factors in this target group of children. (See Table 4 for summary information.)

TABLE 4. Incidences of Pre- and Perinatal Factors by Group Membership*

	HEV		Registry		Community	
Variables	No%	Yes%	No%	Yes%	No%	Yes%
Pre-eclampsia	80	20	92	8	100	0
Chronic Villitis***	58	43	78	22	100	0
Small for Gestational Age	85	15	92	8	100	0
Cesarean Section	58	43	68	32	88	13
Viral Infection	100	0	95	5	100	0
Fetal Distress	78	23	78	22	88	13
Multiple Gestation	93	8	89	11	100	0
Maternal Hypertension**	70	30	86	14	100	0
Maternal Diabetes	95	5	95	5	100	0

* (Percentages may not add up to 100% due to rounding error)

**p < .10

***p < .05

A 43% incidence of chronic villitis was noted in this group of children. As a group, these children had a high incidence of delivery by cesarean section (43%). Fifty percent of the HEV group had some form of hypertensive disease. Maternal hypertension was noted in 30% of the HEV cases and pre-eclampsia was observed in 20%. Both conditions appeared simultaneously in 15% of the group. Chronic maternal disease was noted in a small percentage (five percent) of children with HEV affected placentas. Of these (n=2), maternal diabetes was the sole category. Multiple gestation was noted in eight percent of the cases and fetal distress in 23%.

Fifteen percent were sga. No incidences of documented viral infection were noted in the children with HEV affected placentas.

Statistical Analysis and Findings

The data resulting from the research project was analyzed using the Statistical Package for the Social Sciences. Contrast of the HEV group was made with two control groups; a Registry control group and a community control group, which have elsewhere been described. The relationship between factors in the pre-, peri-, and postnatal environments and group outcome were the focus of this research.

The first step in the analysis of the data was to obtain descriptive statistics. These have been reported for the HEV group in the previous section. This was followed by obtaining correlation coefficients on each variable. A list of these variables can be seen in Tables 5 and 6.

TABLE 5. A List of Continuous Variables of Importance to the Study

childs age in months
maternal age in years
maternal and paternal education in years
income at birth and at present by category
gestational age in weeks
birth weight
ordinal position
smoking in pregnancy
Apgars at one and five minutes
gravida
parity

TABLE 6. A List of Discrete Variables of Importance to the Study

sex
race (white and other)
pre-eclampsia (yes or no)
chronic villitis (yes or no)
small for gestational age (yes or no)
cesarean section (yes or no)
viral infection (yes or no)
fetal distress (yes or no)
multiple gestation (yes or no)
maternal hypertension (yes or no)
maternal diabetes (yes or no)
marital status (married or not married at time of assessment)

All outcome variables were continuous in nature. These included six scales on the MSCA, 13 scales on the PIC-R, nine scales on the DOTS-R, one score on the Bender Gestalt, and one score denoting degree of handicapping conditions (0=none, 1=mild, 2=moderate, 3=severe; to be described more fully in the ensuing discussion). See Table 7 for a complete list of outcome measures and subscales.

TABLE 7. Outcome Measures

McCarthy Scales of Children's Abilities
Verbal
Perceptual-Performance
Quantitative
General Cognitive Index (GCI)
Memory
Motor
Personality Inventory for Children-Revised
Adjustment
Achievement
Intellectual Screening
Development
Somatic Concerns
Depression
Family Relations
Delinquency
Withdrawal
Anxiety
Psychosis
Hyperactivity
Social Skills
Dimensions of Temperament Survey-Revised
Activity Level-General
Activity Level-Sleep
Approach-Withdrawal
Flexibility-Rigidity
Mood (Positivie)
Rhythmicity-Sleep
Rhythmicity-Eating
Rhythmicity-Daily Habits
Task Orientation
Bender Gestalt
Developmental Score (Koppitz)
Degree of Handicapping Conditions
Degree of severity, coded 0 to 3

The chi square statistic and ANOVA were used to examine group differences on the variables. The chi square statistic was used on the discrete variables (see Table 6). The .05 level of significance was established. When assumptions for the chi square statistic were violated (i.e. when minimum expected frequencies were less than five in each cell), the two control groups were pooled to form one group (a Registry/Community control group) which then allowed the chi square statistic to be computed. This had a minimal effect on the results. Chronic villitis was significant at the .05 level of significance ($p=.0267$ and $p=.0281$ in the two control group and the pooled control group analysis respectively). Maternal hypertension neared significance ($p=.0648$ using two control groups and $p=.0572$ using the pooled control group).

ANOVA was used to examine group status with the continuous variables (see Table 5). The Bartlett test for homogeneity of variances was used. The .05 level of significance was set for these analyses. Variances exceeded the level of significance on the Bartlett test for three variables; gestational age, ordinal position, and five minute Apgar scores. Taking the log adequately transformed the variances so they no longer differed significantly for ordinal position and five minute Apgar scores. A variety of transformations failed to equalize the variances on the variable gestational age. This variable had a negative skew that was nearer normal than was true of the untransformed variables of ordinal position and five minute Apgar scores. It appears that the two variables which had a greater degree of skewness and thus differed more from normal were more readily transformed than was gestational

age.

With the completion of these computations, the results were examined for possible confounding variables which could be statistically controlled in the next phase of the analysis. If significant confounding variables of a continuous nature were found, the ANCOVA procedure would be used, which is appropriate when all variables are continuous. If the significant confounds were discrete in nature, then a multi-factor ANOVA would be used since it is appropriate for the analysis of continuous and discrete variables.

Two variables which were significantly related to (or nearly so) group status and outcome measures at the .05 level of significance were noted (i.e. chronic villitis, p=.0267 and maternal hypertension, p=.0572; both using the pooled control group). Both were discrete variables so a three factor ANOVA design was employed to analyze the results.

The next section will attempt to relate the statistical findings to the research in a systematic way. Discussion of each hypothesis in turn and the pertinent data will ensue.

The first two hypotheses will be examined together due to the nature of their statistical analysis which employed a 2 X 3 ANOVA on the variables group and sex.

H1: Those children with HEV affected placentas will do the poorest on outcome measures. The Registry control group will have lower scores than those children in the community control group but not as low as the children in the HEV group.

H2: Male sex will be associated with poorer outcome.

In order to address these hypotheses, it will be most orderly to examine each outcome measure in turn. Focus will begin with the MSCA scales, followed by the PIC-R, DOTS-R, Bender Gestalt, and degree of handicapping conditions.

An examination of Table 8 reveals that on all six scales, the HEV group preformed the poorest of all the groups. The Registry control group did better than the HEV group and the community control group outperformed both groups on all six measures.

TABLE 8. Mean MSCA Scores by Group Membership and Sex*

		HEV	Registry	Community
Verbal	Total	44.26	47.68	52.0
	Male	44.0	47.94	53.0
	Female	44.37	47.45	50.75
Perc.**	Total	44.03	48.53	52.44
	Male	42.09	50.12	55.6
	Female	44.81	47.00	48.5
Quant.	Total	44.87	46.05	49.78
	Male	45.55	45.53	51.2
	Female	44.59	46.5	48.0
GCI	Total	88.79	94.73	102.44
	Male	87.63	95.71	105.4
	Female	89.26	93.90	98.75
Memory**	Total	43.55	47.95	52.67
	Male	41.55	48.24	54.0
	Female	44.37	47.70	51.0
Motor**	Total	44.21	47.62	53.89
	Male	44.82	45.18	57.6
	Female	43.96	49.70	49.25
Group n	Total	38	37	9
	Male	11	17	5
	Female	27	20	4

*mean for GCI=100, all others mean=50
**$p < .05$

Differences were statistically significant on the perceptual-performance, memory, and motor scales at the .05 level of significance on the univariate F test for group effects (see Table 9). All other univariate F tests were nonsignificant. No statistically significant differences by sex were noted.

TABLE 9. Univariate F Tests For Group Effects On The MSCA

	SS	df	MS	F	Sign
Verbal	512.76	2	256.38	1.48	.233
Perc-Perf	677.28	2	338.64	3.14	.049*
Quant.	176.63	2	88.31	1.11	.332
GCI	1585.72	2	792.86	2.24	.113
Memory	749.61	2	374.80	3.23	.045*
Motor	731.84	2	365.92	3.41	.038*

*p < .05

All multivariate effects for the MSCA are nonsignificant as seen in Table 10.

TABLE 10. Multivariate Effects for the MSCA

Wilks lambda	Value	Approx F	Hypoth df	Error df	Sign.
Constant	.025	477.29	6.0	73.0	0.0
Group	.823	1.242	12.0	146.0	.26
Sex	.969	.389	6.0	73.0	.884
Group X Sex	.787	1.55	12.0	146.0	.113

In the three factor ANOVA, all main effects and interaction effects are nonsignificant. However, some of the scales of the MSCA approach significance in the three-way interaction (group status by

chronic villitis by maternal hypertension). The verbal scale notes a p value of .06 and the quantitative scale notes a p value of .073. These nonsignificant findings indicate that the two confounding variables interacting with group membership account for the significant differences noted in the one factor analysis (see Table 11).

TABLE 11. Univariate F Tests for the Three-Way Analysis on the MSCA

Variable	SS	df	MS	F	Sign.
Verbal	608.24	1	608.24	3.65	.06
Perc.-Perf.	102.66	1	102.66	.94	.336
Quant.	253.68	1	253.68	3.30	.073
GCI	1031.81	1	1031.81	2.94	.091
Memory	332.96	1	332.96	2.88	.094
Motor	12.79	1	12.79	.11	.738

All multivariate F tests for the three-way analysis on the MSCA are nonsignificant, as can be seen in Table 12. Means and group size for the three-way analysis can be seen in Tables 13-14.

TABLE 12. Multivariate Effects for the Three-Way Analysis On The MSCA

Source	Value	Approx F	Hypoth df	Error df	Sign
Grp	.862	.875	12.0	136.0	.574
CV	.949	.599	6.0	68.0	.730
HTN	.905	1.186	6.0	68.0	.324
Grp X CV	.934	.801	6.0	68.0	.572
Grp X HTN	.921	.970	6.0	68.0	.452
CV X HTN	.910	1.11	6.0	68.0	.365
Grp X CV X HTN	.917	1.02	6.0	68.0	.418

TABLE 13. Mean MSCA Scores for the Three-Way Analysis

		HEV		Registry		Community	
	CV:	N	Y	N	Y	N	Y
Verb	HTN: N	44.5	42.4	47.6	43.8	51.9	--
	Y	46.3	45.3	41.0	70.0.	--	--
Perc	N	42.6	45.6	48.8	49.0	50.7	--
	Y	42.8	48.3	39.7	55.5	--	--
Quant	N	44.3	47.7	46.2	46.2	50.43	--
	Y	42.9	41.7	38.7	54.5	--	--
GCI	N	87.3	90.1	95.4	92.0	101.71	--
	Y	88.6	91.3	79.7	117.5	--	--
Memory	N	44.3	42.3	47.8	45.5	51.3	--
	Y	45.1	41.0	44.0	63.0	--	--
Motor	N	43.3	45.9	47.2	48.8	50.7	--
	Y	42.9	45.7	45.7	52.0	--	--

TABLE 14. Group Size For The Three-Way Analysis On The MSCA

	HEV		Registry		Community	
CV:	N	Y	N	Y	N	Y
HTN: N	15	12	26	6	7	0
Y	8	3	3	2	0	0

An examination of the PIC-R results reveals a pattern of more extreme scores for the HEV children on several scales, including overall adjustment, achievement, intellectual screening, development, withdrawal, social skills, and psychosis. Only the latter neared statistical significance (p=.0567) using the one factor ANOVA (see Table 15). Elevations greater than two standard deviations were noted on the adjustment and delinquency scales for the HEV group. Both males and females contributed to these elevated scores. Interestingly, the community controls also peaked at over two standard deviations on these same two scales. An analysis of Table 16 reveals that the female community controls contributed to these elevelations more so than did the males. Female community controls also peaked at over two standard deviations above the mean on the anxiety and hyperactivity scales while the males did not. The Registry control group was within the normal range on all but the adjustment scale, where the males were observed to have scores greater than two standard deviations above the mean.

TABLE 15. Univariate F Test For Group Effects on the PIC-R Psychosis Scale

Source	SS	df	MS	F	Sign.
Between Groups	1588.19	2	794.09	3.0	.0567
Within Groups	16923.59	64	264.43		
Total	18511.79	66			

TABLE 16. Mean PIC-R Scale Scores by Group Membership and Sex*

Variable		HEV	Registry	Community
Adj	Total	74.0**	68.7	71.3**
	Male	80.1**	73.1**	65.0
	Female	71.0**	64.5	81.7**
Ach	Total	61.6	56.1	54.5
	Male	61.0	54.9	55.4
	Female	61.9	57.3	53.0
IS	Total	65.9	64.7	59.4
	Male	66.1	64.4	57.4
	Female	65.8	64.9	62.7
Dvl	Total	59.0	56.4	52.1
	Male	59.1	54.9	53.8
	Female	59.0	57.8	49.3
Som	Total	59.7	60.4	56.0
	Male	66.1	60.4	54.8
	Female	56.6	60.3	58.0
Dep	Total	59.7	59.6	59.8
	Male	61.7	56.2	56.0
	Female	58.7	62.7	66.0
Fam	Total	59.0	57.6	60.6
	Male	66.2	59.9	63.2
	Female	55.5	55.3	56.3
Dlq	Total	71.2**	63.9	73.1**
	Male	74.8**	63.5	65.6
	Female	69.4	64.2	85.7**
Wdl	Total	61.5	57.3	57.1
	Male	63.6	56.1	55.2
	Female	60.5	58.4	60.3
Anx	Total	62.4	59.2	65.0
	Male	66.0	58.0	58.2
	Female	60.7	60.4	76.3**
Psy	Total	64.7	58.3	49.8
	Male	65.6	55.1	54.0
	Female	64.3	61.2	42.7
Hyp	Total	59.9	59.5	67.9
	Male	63.6	64.4	64.6
	Female	58.1	54.9	73.3**
SSK	Total	57.0	56.1	55.0
	Male	56.0	52.7	53.4
	Female	57.5	59.2	57.7
Grp n	Total	30	29	8
	Male	10	14	5
	Female	20	15	3

*Scores are T scores, with a normal range of 30T to 70T
**greater than two standard deviations above the mean

All of the multivariate analyses were nonsignificant (see Table 17).

TABLE 17. Multivariate Effects For The PIC-R

Wilks lambda	Value	Approx F	Hypoth df	Error df	Sign.
Constant	.004	701.19	16.0	46.0	0.0
Grp	.567	.942	32.0	92.0	.562
Sex	.738	1.02	16.0	46.0	.453
Grp X Sex	.643	.708	32.0	92.0	.865

The three factor ANOVA revealed group membership and maternal hypertension to be relatively less important in accounting for significant differences on outcome measures than was chronic villitis. An examination of Tables 18-20 indicates that presence of chronic villitis, regardless of group membership and across both levels of maternal hypertension, significantly correlated to higher scores on the adjustment and delinquency scales of the PIC-R at the .05 level of statistical significance. Higher scores on the PIC-R indicate heightened concern and greater problems in these areas according to parental report. Nearing significance, and correlating in the same direction were the scales of somatic concern and anxiety ($p=.062$ and $p=.063$ respectively).

TABLE 18. Univariate F Tests For Chronic Villitis On The PIC-R

Variable	SS	df	MS	F	Sign.
Adj	1885.32	1	1885.32	6.11	.017*
Ach	430.16	1	430.16	2.03	.159
IS	96.12	1	96.12	.43	.516
Dvl	61.71	1	61.71	.29	.588
Som	899.48	1	899.48	3.64	.062
Dep	418.86	1	418.86	1.73	.193
Fam	164.66	1	164.66	.56	.457
Dlq	1433.62	1	1433.62	7.36	.009*
Wdl	271.78	1	271.78	1.42	.238
Anx	865.46	1	865.46	3.58	.063
Psy	446.71	1	446.71	1.58	.213
Hpr	492.84	1	492.84	2.78	.101
SSK	46.99	1	46.99	.35	.556

*p < .05

TABLE 19. Univariate F Tests For Group Effects On The PIC-R

Variable	SS	df	MS	F	Sign.
Adj	847.78	2	423.89	1.37	.262
Ach	265.61	2	132.80	.63	.537
IS	106.66	2	53.33	.24	.789
Dvl	314.85	2	157.43	.76	.474
Som	113.54	2	56.77	.23	.795
Dep	95.91	2	47.95	.19	.821
Fam	205.74	2	102.85	.35	.706
Dlq	1646.19	2	823.10	4.23	.019*
Wdl	149.28	2	74.64	.39	.679
Anx	351.67	2	175.84	.73	.487
Psy	1524.57	2	762.29	2.70	.076
Hpr	1416.91	2	708.46	4.00	.024*
SSK	6.35	2	3.17	.02	.977

*p < .05

TABLE 20. Univariate F Tests For Maternal Hypertension On The PIC-R

Variable	SS	df	MS	F	Sign.
Adj	124.70	1	124.70	.40	.528
Ach	780.91	1	780.91	3.70	.060
IS	1.48	1	1.48	.006	.936
Dvl	1305.03	1	1305.03	6.28	.015*
Som	2.48	1	2.48	.01	.921
Dep	17.51	1	17.51	.07	.789
Fam	54.24	1	54.24	.18	.669
Dlq	417.59	1	417.59	2.15	.149
Wdl	107.81	1	107.81	.56	.456
Anx	203.38	1	203.38	.84	.363
Psy	21.26	1	21.26	.08	.785
Hpr	168.62	1	168.62	.95	.333
SSK	191.00	1	191.00	1.42	.238

*p < .05

Group membership was significantly associated with the delinquency and hyperactivity scales of the PIC-R (however, it must be remembered that since this is an unbalanced design, group effects, which are the second variable in the design, are not independent of chronic villitis effects, which are the first variable in the design). Children in the HEV group tended to have more parental concerns in the delinquency dimension whereas the Registry control group had greater problems with hyperactivity. Approaching significance (p=.076) was the psychosis scale, with HEV children possessing the higher scores.

Interestingly, absence of maternal hypertension during pregnancy was significantly associated with poorer outcome (or higher scores) on the development scale of the PIC-R and approached significance (p=.06) on the achievement scale.

The average scores and group size for this three-way analysis can be viewed in Tables 21-22.

TABLE 21. Mean PIC-R Scores For The Three-Way Analysis

		HEV		Registry		Community	
	CV:	N	Y	N	Y	N	Y
Adj HTN:	N	64.6	80.5*	65.4	77.8*	78.83*	--
	Y	71.8*	83.0*	71.0*	73.5*	--	--
Ach	N	63.6	63.8	55.7	66.2	56.0	--
	Y	54.0	58.3	47.3	48.5	--	--
IS	N	65.8	68.2	62.0	70.4*	60.2	--
	Y	68.0	53.3	71.0*	66.5	--	--
Dvl	N	63.9	60.7	57.1	63.2	50.7	--
	Y	50.4	50.7	48.7	45.0	--	--
Som	N	53.3	64.8	58.4	70.0*	56.8	--
	Y	56.4	66.3	63.3	51.0	--	--
Dep	N	55.9	65.3	57.4	65.0	61.0	--
	Y	54.2	59.3	68.3	53.5	--	--
Fam	N	58.6	60.0	56.6	54.8	64.3	--
	Y	61.8	52.0	74.3*	48.0	--	--
Dlq	N	62.9	76.0*	58.7	75.8*	79.3*	--
	Y	75.0*	73.0*	70.7*	72.5*	--	--
Wdl	N	57.2	68.8	57.7	54.4	58.2	--
	Y	55.6	56.3	65.7	50.5	--	--
Anx	N	54.0	68.3	55.5	67.6	65.7	--
	Y	62.2	67.3	75.0*	50.5	--	--
Psy	N	66.0	66.8	56.9	59.0	46.0	--
	Y	57.6	64.0	66.3	57.5	--	--
Hpr	N	53.4	62.6	56.8	68.2	73.0*	--
	Y	63.6	65.0	55.0	69.0	--	--
SSK	N	54.9	59.8	57.5	57.0	56.7	--
	Y	55.0	56.0	49.7	50.0	--	--

* greater than two standard deviations above the mean

TABLE 22. Group Size For The Three-Way Analysis On The PIC-R

		HEV		Registry		Community	
	CV:	N	Y	N	Y	N	Y
HTN:	N	10	12	19	5	6	0
	Y	5	3	3	2	0	0

All of the multivariate tests of significance failed to reach statistical significance (see Table 23).

TABLE 23. Multivariate F Tests For The Three-Way Analysis On The PIC-R

Source	Value	Approx. F	Hypoth. df	Error df	Sign.
CV	.662	1.31	16.0	41.0	.239
Grp	.569	.835	32.0	82.0	.711
HTN	.647	1.40	16.0	41.0	.189
Grp X CV	.785	.701	16.0	41.0	.776
Grp X HTN	.674	1.24	16.0	41.0	.281
CV X HTN	.678	1.22	16.0	41.0	.298
Grp X CV X HTN	.805	.62	16.0	41.0	.848

No clear pattern of group or sex differences were apparent on the DOTS-R. The HEV group scored between the two control groups in terms of general activity level, with the Registry control group being the most active. The HEV group exhibited the most approach behavior of the three groups, the least regularity in sleeping and less persistence in task orientation. Quality of mood, flexibility/rigidity, and rhythmicity daily habits were comparable for all groups (see Table 24). None of these differences were statistically significant. Table 25 reveals the one significant correlation ($r=-.31$, $p < .05$) of temperament with sex on the rhythmicity-sleep dimension, which favored males.

TABLE 24. Mean DOTS-R Dimensions By Group Membership And Sex

		HEV	Registry	Community
Act-Gen	Total	19.0	20.4	16.1
	Male	21.1	20.6	15.6
	Female	17.7	19.9	17.5
Act-Sl	Total	9.0	10.1	8.4
	Male	9.1	9.8	9.4
	Female	8.9	10.6	6.0
App/Wdl	Total	21.2	20.6	18.9
	Male	21.4	19.9	20.2
	Female	21.0	21.9	15.5
Flex/Rig	Total	16.3	16.6	16.4
	Male	15.3	16.5	16.8
	Female	16.9	16.7	15.5
Mood	Total	25.9	25.1	25.29
	Male	25.6	25.8	26.8
	Female	26.1	23.7	21.5
Rhy-Sl	Total	16.9	18.3	18.6
	Male	18.4	18.5	20.0
	Female	15.9	17.9	15.0
Rhy-Eat	Total	15.3	14.8	17.0
	Male	15.9	14.5	18.8
	Female	14.9	15.4	12.5
Rhy-Hab	Total	13.5	13.9	14.1
	Male	13.9	14.2	14.2
	Female	13.2	13.3	14.0
Task	Total	45.6	46.9	49.7
	Male	48.2	47.1	53.0
	Female	43.9	46.6	41.5
Grp n	Total	23	20	7
	Male	9	13	5
	Female	14	7	2

TABLE 25. Correlation Coefficients of Sex To The DOTS-R Dimensions

Act-Gen	Act-Sl	App	Flex	Mood	Rhy-Sl	Rhy-Eat	Rhy-Hab	Task
-.15	-.06	.03	.12	-.14	-.31*	-.13	-.13	-.23

* $p < .05$

Analysis using the three factor ANOVA pointed to slightly different results. For mean scores and group size for the three-way analysis, see Tables 26-27. The main effects of maternal hypertension were statistically significant for one of the dimensions; approach-withdrawal. This indicates that regardless of group membership, or presence or absence of chronic villitis, those children with maternal hypertension present during gestation exhibit greater approach behavior than those without maternal hypertension. Of the nine DOTS-R dimensions, five of these reached statistical significance in the group by maternal hypertension interaction at the .05 level of significance. This indicates that on a certain level of maternal hypertension, there was a difference by group membership on certain outcome variables. Specifically, the HEV group with maternal hypertension present during pregnancy had lower scores (reflecting less of the dimension according to parental report) on the following scales than those without maternal hypertension: (positive) mood, rhythmicity-sleep, rhythmicity-daily habits, and task-orientation. The Registry control group had higher scores on these same scales in the presence of maternal hypertension compared to those without maternal hypertension. Higher scores on the activity level-general dimension were received by the HEV children with maternal hypertension as compared to those without maternal hypertension. The Registry control group scored in the opposite direction on this dimension (see Tables 28-29).

TABLE 26. Mean DOTS-R Dimensions For The Three Way Analysis

			HEV		Registry		Community	
		CV:	N	Y	N	Y	N	Y
Act-G	HTN:	N	16.0	17.6	21.5	20.3	16.2	--
		Y	22.4	23.0	18.0	18.0	--	--
Act-Sl		N	8.8	8.3	10.5	11.3	7.8	--
		Y	9.6	10.7	8.3	8.0	--	--
App		N	20.8	19.7	20.2	20.0	18.6	--
		Y	23.4	23.3	20.7	24.0	--	--
Flex		N	17.5	15.8	16.5	16.0	15.8	--
		Y	15.4	17.7	17.3	17.0	--	--
Mood		N	27.3	26.2	25.9	20.8	25.2	--
		Y	25.0	24.3	27.0	26.0	--	--
Rhy-Sl		N	18.0	18.1	18.2	15.5	18.8	--
		Y	14.2	15.3	20.0	21.5	--	--
Rhy-Eat		N	15.8	15.9	14.4	13.0	16.4	--
		Y	13.8	14.7	16.7	18.0	--	--
Rhy-Hab		N	14.3	14.0	13.9	11.8	16.4	--
		Y	12.8	11.7	16.3	14.0	--	--
Task		N	48.0	48.0	46.5	40.3	51.6	--
		Y	40.8	41.7	53.0	53.5	--	--

TABLE 27. Group Size For The Three Way Analysis On The DOTS-R

		HEV		Registry		Community	
	CV:	N	Y	N	Y	N	Y
HTN:	N	4	11	11	4	5	0
	Y	5	3	3	2	0	0

TABLE 28. Univariate F Tests For Maternal Hypertension Effects On The DOTS-R

Variable	SS	df	MS	F	Sign.
Act-General	43.08	1	43.08	1.99	.166
Act-Sleep	.01	1	.01	.00	.984
App/Wdl	84.69	1	84.69	4.32	.044*
Flex/Rig	1.42	1	1.42	.23	.636
Mood	.00	1	.00	.00	.997
Rhy-Sleep	9.31	1	9.31	.63	.431
Rhy-Eat	.26	1	.26	.02	.896
Rhy-Dly Hab	2.84	1	2.84	.37	.548
Task Orient	17.89	1	17.89	.24	.630

*$p < .05$

TABLE 29. Univariate F Tests For Group by Maternal Hypertension Interaction Effects On The DOTS-R

Variable	SS	df	MS	F	Sign.
Act-General	163.06	1	163.06	7.53	.009**
Act-Sleep	35.60	1	35.60	3.22	.081
App/Wdl	3.93	1	3.93	.20	.657
Flex/Rig	2.00	1	2.00	.32	.574
Mood	43.93	1	43.93	4.18	.048*
Rhy-Sleep	88.81	1	88.81	6.03	.019*
Rhy-Eat	48.33	1	48.33	3.28	.078
Rhy-Dly Hab	37.19	1	37.19	4.81	.034*
Task Orient	505.11	1	505.11	6.64	.014*

*p < .05

**p < .01

An examination of Table 30 reveals that the HEV group showed a greater immaturity on tasks of a perceptual motor nature than the other two groups. However, since this group is slightly younger, these results must be interpreted cautiously. Males had slightly lower scores (indicating more mature skills), however the differences were nonsignificant. Age equivalencies for all groups reveal relatively mature perceptual motor functioning when compared to age group norms.

TABLE 30. Mean Bender Gestalt Developmental Scores By Group And Sex

		HEV	Registry	Community
Developmental Score	Total	11.26	9.76	9.88
	Male	11.0	9.07	9.5
	Female	11.35	10.31	10.25
Mean Age in Months		63.2	64.38	67.11
Mean Age Equivalency in Months		64-65	66-68	66-68
Group n	Total	30	29	8
	Male	7	13	4
	Female	23	16	4

All analyses of interaction and main effects on the group by sex ANOVA and on the three-way ANOVA were nonsignificant at the .05 level (see Tables 31-32).

TABLE 31. Tests Of Significance For The Bender Gestalt Using Sequential Sums of Squares For Group And Sex

Source	SS	df	MS	F	Sign.
Within Cells	661.33	61	10.84		
Constant	7313.43	1	7313.43	674.58	0.0
Grp	36.52	2	18.26	1.68	.194
Sex	10.29	1	10.29	.95	.334
Grp X Sex	2.44	2	1.22	.112	.894

TABLE 32. Tests of Significance for the Bender Gestalt Using Sequential Sums of Squares For The Three-Way Analysis

Source	SS	df	MS	F	Sign.
Within Cells	619.95	56	11.07		
Constant	7197.79	1	7197.79	650.18	0.0
Group Membership	33.54	2	16.77	1.52	.229
Chronic Villitis	.31	1	.31	.03	.867
Maternal Hypertension	6.16	1	6.16	.56	.459
Group by Chronic Villitis	6.86	1	6.86	.62	.434
Group by Maternal Hypertension	3.39	1	3.39	.31	.582
Chronic Villitis by Maternal Hypertension	7.35	1	7.35	.66	.419
Group by Chronic Villitis by Maternal Hypertension	2.66	1	2.66	.24	.626

Table 33 summarizes the mean Bender Gestalt scores for the three-way analysis.

TABLE 33. Mean Bender Gestalt Scores For The Three-Way Analysis

		HEV		Registry		Community	
	CV:	N	Y	N	Y	N	Y
Bender HTN:	N	11.07	11.14	9.73	8.75	10.5	--
	Y	11.0	14.0	12.0	11.0	--	--
Group n	N	14	7	23	4	6	0
	Y	7	2	1	1	0	0

Handicapping conditions were coded zero through three with

zero corresponding to no handicapping conditions, one indicating mild handicaps, two indicating moderate handicaps, and three indicating severe handicaps. In all, ten children, or approximately 12% of the sample had some degree of handicapping condition. Six percent were considered severely handicapped. The results of this research were not used to determine presence of handicapping conditions (i.e. a low GCI on the MSCA did not suggest a score above zero on this continuum). Rather, previous diagnoses and degree of normal functioning at home and in the school setting determined the score assigned.

TABLE 34. Degree Of Handicap By Group Membership

	HEV		Registry	
	#	%	#	%
None	34	85	33	89
Mild	2	5	3	8
Moderate	0	0	0	0
Severe	4	10	1	3

A score of one was assigned where only one sensory modality or limb was affected and the child was able to function with minimal support in a normal school setting.

HEV children with the following conditions were coded one:

a) left ear mild to moderately severe hearing loss

b) high frequency hearing loss

Registry control children coded one included:

a) right hand amputation due to injury

b) mild mental retardation

c) very mild heart defect (ventricular septal defect) which did not restrict activity.

No children in either group received a score of two which was designated for situations where one or more sensory modalities or limbs were affected and moderate assistance was needed to function in the home or regular classroom. A score of three was assigned where much educational or home assistance was needed due to multiple or very severe sensory losses or physical handicaps.

The following HEV children received this score:

a) spina bifida with milomengiocele

b) spastic quadraplegia, legally blind in left eye

c) multiple physical handicaps, trainable mentally impaired

d) downs syndrome, microcephaly (greater than expected for downs)

The following Registry control children received a score of three:

a) profoundly hearing impaired, heart defect, cataract on right eye, legally blind in right eye, vision 20/80 in left eye.

Table 35 summarizes mean handicapping conditions by group and sex, revealing a greater degree of handicap in the HEV group. These differences are nonsignificant as seen in Table 36.

TABLE 35. Mean Handicap Scores By Group And Sex

		HEV	Registry	Community
Handicap	Total	.42	.16	0
	Male	.33	.06	0
	Female	.46	.25	0
Group n	Total	40	37	9
	Male	12	17	5
	Female	28	20	4

TABLE 36. Tests of Significance For Handicap Using Sequential Sums Of Squares For Group And Sex

Source	SS	df	MS	F	Sign.
Within Cells	50.32	80	.63		
Constant	6.15	1	6.15	9.78	.002
Grp	2.05	2	1.02	1.63	.203
Sex	.41	1	.41	.65	.421
Grp X Sex	.07	2	.03	.05	.947

On the three factor ANOVA, only the interaction effects of group membership by chronic villitis by maternal hypertension approached significance (p=.061) as can be seen in Table 37. Table 38 summarizes the means for the three-way analysis.

TABLE 37. Tests Of Significance For Handicap Using Sequential Sums Of Squares For The Three-Way Analysis

Source	SS	df	MS	F	Sign.
Within	45.17	75	.60		
Constant	6.30	1	6.30	10.46	.002
Group Membership	1.90	2	.95	1.58	.213
Chronic Villitis	.14	1	.14	.23	.636
Maternal Hypertension	.66	1	.66	1.09	.299
Group by Chronic Villitis	1.48	1	1.48	2.45	.122
Group by Maternal Hypertension	.00	1	.00	.00	.970
Chronic Villitis by Maternal Hypertension	1.18	1	1.18	1.96	.166
Group by Chronic Villitis by Maternal Hypertension	2.18	1	2.18	3.62	.061

TABLE 38. Mean Handicap Score For The Three-Way Analysis

		HEV		Registry		Community	
	CV:	N	Y	N	Y	N	Y
Handicap HTN	N	.73	.23	.08	.67	0	--
	Y	0.0	.75	0.0	0.0	--	--
Group n	N	15	13	26	6	7	0
	Y	8	4	3	2	0	0

When normal and abnormal outcomes (abnormal is herein defined as less than two standard deviations below the mean on the MSCA and Bender-Gestalt and greater than two standard deviations above the mean on the PIC-R) are analyzed by group membership, very few

differences are noted regarding percentage of normal and abnormal outcomes, as can be seen in the following table.

TABLE 39. Normal and Abnormal Outcomes by Group Membership

	HEV		Registry		Community	
	#	%	#	%	#	%
Normal	14	35	11	29.7	3	33.3
Abnormal	26	65	26	70.3	6	66.7
MSCA	11	27.5	8	21.6	0	0
PIC-R	25	62.5	22	59.5	6	66.7
Bender	0	0	0	0	0	0
MSCA and PIC-R	10	25	4	10.8	0	0

However, the table reveals that the HEV group has a higher proportion of children with poorer functioning in both cognition and personality. Interestingly, the community control group exceeds both the HEV and Registry groups in proportion of elevated PIC-R scores.

Tables 40 and 41 examine normal and abnormal outcomes. Table 40 breaks this down according to chronic villitis, maternal hypertension, both, or other associations. As can be evidenced, a high proportion of abnormal scores occur with chronic villitis across groups. Interestingly, for the HEV group, a 65.4% incidence of abnormal scores occur where chronic villitis, maternal hypertension, or both are present. In the Registry control group this figure is 34.6%. Table 41 looks at specific outcome measures

by incidence of HEV, chronic villitis (CV), and maternal hypertension (HTN).

TABLE 40. Normal and Abnormal Group Outcomes by Chronic Villitis and Maternal Hypertension and Other Associations

	HEV		Registry	
Outcomes	#	%	#	%
Normal with Chronic Villitis	3	25	1	16.7
Abnormal with Chronic Villitis	9	75	5	83.3
Normal with Hypertension	4	44.4	1	25
Abnormal with Hypertension	5	55.6	3	75
Normal with Both	0	0	0	0
Abnormal with Both	3	100	1	100
Abnormal with Chronic Villitis, Hypertension, or Both	17	65.4	9	34.6
Abnormal with Other Unknown Associations	9	34.6	17	65.4

TABLE 41. Normal and Abnormal Outcome by HEV, Chronic Villitis, and Maternal Hypertension

	MSCA		PIC-R		Bender		Handicap	
	%	n	%	n	%	n	%	n
HEV Normal	72.5	29	37.5	15	100	40	85	34
HEV Abnormal	27.5	11	62.5	25	0	0	15	6
HEV + CV Normal	66.6	8	18	2	100	7	91.6	11
HEV + CV Abnormal	33.3	4	82	9	0	0	8.3	1
CV Normal	66.6	4	20	1	100	4	66.6	4
CV Abnormal	33.3	2	80	4	0	0	33.3	2
HEV + HTN Normal	87.5	7	20	1	100	6	100	8
HEV + HTN Abnormal	12.5	1	80	4	0	0	0	0
HTN Normal	60	3	0	0	100	2	80	4
HTN Abnormal	40	2	100	5	0	0	20	1
HTN + CV Normal	100	1	0	0	100	1	100	1
HTN + CV Abnormal	0	0	100	1	0	0	0	0
HEV + CV + HTN Normal	100	0	0	0	100	2	100	3
HEV + CV + HTN Abnormal	0	0	100	3	0	0	0	0

H3: Certain factors in the pre-, peri-, and /or postnatal environments will correlate to poorer prognosis. These factors include the presence of chronic maternal disease (diabetes in this study, coded D in Tables 42, 43 and 44), multiple gestation (MG), fetal distress (FD), cesarean section (CS), maternal hypertensive disease (HT), pre-eclampsia (PE), smoking in pregnancy (SM), low birth weight (BW), early gestation (GA), increased maternal age (MA), greater ordinal position (OP), increased gravida (GR) and parity (PA), disrupted marital status (M for married, DI for divorced, S for single and SE for seperated), and minority group membership (RA).

Certain factors in the pre-, peri-, and postnatal environments were found to correlate significantly to poorer prognosis at the .05 level of statistical significance on various outcome measures. In general, those children tending to do better on the various outcome measures tended to be white, born to mothers who refrained from or decreased their smoking during pregnancy, had a relatively higher birth weight, and had no or few risk factors during pregnancy or complications at birth.

Consumption of alcohol by mothers was difficult to measure and so was not statistically analyzed. None of the mothers reported excessive alcohol use (heavy drinking or daily consumption). Nine mothers reported occasional use, ranging from one drink a month to one drink a week. Type of drink and ounces were not reported, making comparison difficult.

Table 42 reveals the correlations of factors in the pre-, peri-, and postnatal environments to the MSCA scales. As can

be noted, multiple gestation and being married at time of assessment each correlated significantly to four of the scales, while birth weight correlated significantly to all but the Verbal scale.

TABLE 42. Correlation Coefficients of Pre-, Peri-, and Postnatal Factors to the MSCA

Variables	Verbal	Perceptual-Performance	Quantitative	GCI	Memory	Motor
RA	-.15	-.25*	-.15	-.22*	-.04	-.27*
MA	.17	.11	.17	.16	.15	.11
GA	.14	.07	.15	.12	.12	.17
BW	.19	.35***	.37***	.30**	.22*	.35***
OP	-.05	-.07	-.08	-.07	-.00	.05
SM	-.23*	-.11	-.24*	-.23*	-.16	-.05
PE	-.09	-.25*	-.22*	-.19	-.11	-.17
CS	-.10	-.02	-.08	-.077	-.14	-.25*
FD	.04	-.02	.03	.01	.07	-.20
MG	-.12	-.21*	-.29**	-.21*	-.22*	-.18
HT	.06	-.09	-.15	-.05	-.00	-.07
D	-.13	-.04	-.10	-.12	-.20	-.03
GR	.08	-.13	-.49	-.05	.31	.36
PA	-.08	.59	-.58	-.08	.08	.58
M	.18	.32**	.25*	.29**	.08	.28**
S	-.17	-.29**	-.17	-.25*	-.07	-.15
DI	-.10	-.20	-.17	-.18	-.12	-.25*
SE	-.02	-.01	-.06	-.02	.09	-.01

*p < .05
**p < .01
***p < .001

No clear patterns emerged between the PIC-R, DOTS-R, Bender Gestalt, or degree of handicapping conditions with factors in the pre-, peri-, or postnatal environments (see Tables 43-45). Interestingly, presence of maternal diabetes significantly and positively correlated to four scales on the PIC-R: somatic concerns, depression, family relations and anxiety at the .05 level of statistical significance. Degree of smoking during pregnancy correlated negatively to two DOTS-R dimensions: mood (positive) and rhythmic sleep patterns. Two factors were found to significantly correlate to degree of handicapping conditions: birth weight and fetal distress.

TABLE 43. Correlation Coefficients of Pre-, Peri-, and Postnatal Factors to the PIC-R Scales

	Adj	Ach	IS	Dvl	Som	D	Fam	Dlq	Wdl	Anx	Psy	Hpr	SSK
RA	-.13	.08	.05	.05	-.11	.09	-.22	.03	.04	.03	.08	-.22	.19
MA	.01	.03	.06	.11	-.11	-.20	-.44**	.0	-.12	-.16	.05	-.03	.06
GA	.01	.03	-.06	.01	-.15	-.01	-.08	.01	.03	-.03	.03	.05	.10
BW	.01	-.05	-.17	-.20	-.17	.00	-.01	.06	-.00	.07	-.30*	.24	.01
OP	.01	.12	-.05	.10	-.16	-.27	-.08	.17	-.07	-.13	-.11	.13	.02
SM	.04	.13	-.04	.09	.04	.03	.03	.10	.01	.04	.10	.10	.13
PE	.09	-.13	.00	-.11	.03	.02	.08	.04	-.04	.17	.18	-.02	-.07
CS	.03	.05	.01	.06	.17	.04	-.17	-.02	.09	.03	.20	-.10	.11
FD	-.09	-.11	-.04	.0	-.09	-.14	-.25*	-.30*	-.17	-.20	.15	-.11	-.09
MG	-.05	-.06	.09	.05	.23	.00	.10	-.16	-.12	.04	.16	-.20	-.17
HT	.08	-.20	.02	-.26*	.00	-.03	.05	.15	-.07	.11	.03	.07	-.13
D	.06	-.04	.09	-.00	.24*	.25*	.31*	-.10	.10	.30*	.15	.01	-.05
GR	.50	.31	.49	.24	-.19	-.09	.56	.65	.19	-.10	---	.28	-.12
PA	.74	.83*	.62	.74	.62	.11	---	.83*	.53	.44	.41	.41	.41
M	.08	-.05	-.14	-.12	.17	.00	-.55**	.19	.21	.15	-.04	.03	.11
S	-.13	-.13	-.03	-.10	-.07	.09	.10	-.15	.08	.01	.13	-.29	.05
DI	-.03	.06	.12	.13	-.10	.03	.54**	-.17	-.17	-.10	.07	.03	-.08
SE	-.03	.09	.11	.09	-.14	-.13	.06	.03	-.20	-.13	-.15	.07	-.12

*p < .05
**p < .001

TABLE 44. Correlation Coefficients of Pre-, Peri-, and Postnatal Factors to tne DOTS-R Dimensions

	Act-G	Act-S	App	Flex	Mood	Rhy-S	Rhy-E	Rhy-H	Task
RA	-.15	-.06	.04	.12	-.14	-.31*	-.13	-.13	-.23
MA	.29*	.12	.17	.02	.16	-.10	.01	-.20	-.10
GA	-.20	-.23	-.00	.05	.19	-.12	-.25	-.16	-.21
BW	-.19	.04	.04	.18	.13	.10	-.11	.02	.00
OP	.31*	.06	.16	-.08	.14	-.15	-.00	-.09	-.10
SM	.13	-.09	.01	-.00	-.33*	-.34*	-.16	-.16	-.27
PE	.32*	.01	.22	.10	.09	-.06	-.05	-.02	-.05
CS	.06	-.33*	-.05	-.15	.04	.13	-.09	-.02	.02
FD	.18	-.18	.18	.11	.20	.01	-.03	.08	.02
MG	.08	-.05	-.12	-.26	.01	.15	-.16	.05	.02
HT	.21	.01	.31*	.06	-.01	-.12	.01	-.06	-.07
D	.04	-.12	-.10	-.11	-.09	.08	-.18	-.11	-.08
GR	---	.50	.87	.87	.87	-.50	---	.87	---
PA	.87	-.10**	-.87	-.87	-.87	-.50	-.87	-.87	-.87
M	.06	.14	-.10	-.08	-.07	-.06	-.17	-.17	-.15
DI	-.06	-.25	.11	.08	.17	.13	.18	.28*	.22
SE	-.01	.18	-.01	.01	-.19	-.12	.02	-.18	-.10

*p < .05
**p < .001

TABLE 45. Correlation Coefficients of Pre-, Peri-, and Postnatal Factors to the Bender Gestalt and Handicap

Variables	Bender Gestalt	Degree Handicap
Race	.09	.14
Mat. Age	.14	.08
GA	.02	-.05
Birth Wt.	-.14	-.32**
Ord. Pos.	.07	-.02
Smking	.10	.01
Pre-eclampsia	.10	.00
C Section	.01	.18
FD	.01	.30**
Mult. Gest.	.14	-.10
Mat. Htn.	.16	-.06
Diabetes	-.11	-.08
Gravida	---	-.14
Parity	.42	.06
MS: M	-.16	-.07
Sin	.10	.21
Div	.08	-.00
Sep	.08	-.08

**p < .01

H4: Socio-economic variables will be positively correlated to outcome.

Those socio-economic variables examined in this phase of the analysis included parental education level and income at birth and at time of assessment. The former was measured in completed years of education. The latter was measured by the following categories:

A=0-$5,000	E=$20,000-$25,000
B=$5,000-$10,000	F=$25,000-$30,000
C=$10,000-$15,000	G=$30,000-$35,000
D=$15,000-$20,000	H=$35,000+

As can be seen from Table 46, there were no significant differences by group on any of these socio-economic variables.

TABLE 46. Mean Socio-Economic Variables By Group Membership

	HEV	Registry	Community	F	Sign.
Maternal Ed	12.58	12.81	13.14	.25	.78
Paternal Ed	12.97	12.86	13.71	.25	.77
Income/Birth	4.48	4.46	4.29	.03	.97
Income/Assess	5.2	4.76	5.14	.40	.67

Correlation coefficients to outcome measures can be viewed in Tables 47 through 50.

TABLE 47. Correlation Coefficients for Socio-Economic Variables and the MSCA Scales

MSCA	Mat. Ed.	Pat. Ed.	Income/ Birth	Income/ Assess
Verbal	.42***	.25*	.12	.19
Perc. Perf.	.41***	.24*	.24*	.36***
Quantitative	.52***	.36***	.17	.32**
GCI	.49***	.29**	.21	.31**
Memory	.38***	.24*	.03	.13
Motor	.17	.08	.14	.17

*p < .05

**p < .01

***p < .001

As is apparent from the preceeding table, parental education correlated significantly to five of the six MSCA scales. Of the two levels of education, maternal education had a correlation of a stronger magnitude than did paternal education.

TABLE 48. Correlation Coefficients for Socio-Economic Variables and the PIC-R Scales

PIC-R Scales	Mat. Ed.	Pat. Ed.	Income/ Birth	Income/ Assess
Adj	-.11	.01	.06	.05
Ach	-.22	-.14	-.06	-.09
IS	.07	-.01	.02	.01
Dvl	-.14	-.05	-.17	.14
Som	-.01	.05	.11	.11
Dep	-.05	-.18	-.08	-.00
Fam	-.33**	-.35**	-.26*	-.58***
Dlq	-.13	-.09	.15	.09
Wdl	-.17	-.12	.10	.07
Anx	-.19	-.17	-.08	.04
Psy	-.04	.14	-.08	-.09
Hpr	-.02	-.09	.17	.14
SSK	-.13	-.14	-.07	.02

*p < .05

**p < .01

***p < .001

It is apparent from TABLE 48 that socio-economic variables are negatively correlated to family problems as assessed on the family relations scale of the PIC-R.

As can be seen in the following table, only parental education correlates significantly on the DOTS-R.

TABLE 49. Correlation Coefficients for Socio-Economic Variables and the DOTS-R Dimensions

DOTS-R Dimensions	Mat. Ed.	Pat. Ed.	Income/ Birth	Income/ Assess
Act-General	-.14	-.14	.02	-.06
Act-Sleep	.07	.05	.04	.11
App/Wdl	.08	-.10	.14	-.05
Flex/Rig	.01	.01	.19	.07
Mood	.10	.13	.22	.09
Rhy-Sleep	.41**	.31*	-.01	-.02
Rhy-Eating	.31*	.20	-.03	-.03
Rhy-Dly Hab	.10	.14	-.03	-.08
Task Orient	.34*	.27	-.03	-.05

*p < .05

**p < .01

TABLE 50. Correlation Coefficients for Socio-Economic Variables and the Bender Gestalt and Handicap

Variables	Mat. Ed.	Pat. Ed.	Income/ Birth	Income/ Assess
Bender Gestalt	-.17	-.03	-.05	.05
Handicap	.06	.11	-.13	-.08

A review of Table 50 indicates that none of the socio-economic variables correlate significantly to the Bender Gestalt or degree of handicap.

H5: Presence of fetal growth retardation will be associated with lower scores. Additionally, early onset of delayed fetal

growth will correlate to poorer outcome than will late onset of fetal growth retardation.

The presence of fetal growth retardation (as assessed by the Colorado Intrauterine Growth Chart) was found to correlate significantly to three outcome measures: the MSCA motor scale, the PIC-R psychosis scale, and degree of handicap. The magnitude and direction of these correlations can be seen in the following table.

TABLE 51. Correlation of Small For Gestational Age Infants with Outcome Measures

MSCA		PIC-R		DOTS-R		Bender	Handicap
Scale	r	Scale	r	Scale	r	r	r
Ver	-.10	Adj	.15	Act-G	-.21	.15	.42**
Perc	-.20	Ach	.08	Act-S	-.24		
Quan	-.19	IS	.15	App	-.04		
GCI	-.16	Dvl	.22	Flex	-.19		
Mem	-.10	Som	.10	Mood	.01		
Mot	-.31*	Dep	.02	Rhy-S	.17		
		Fam	.01	Rhy-E	.07		
		Dlq	.03	Rhy-H	-.07		
		Wdl	.10	Task	.08		
		Anx	-.16				
		Psy	.41**				
		Hpr	-.19				
		SSK	.06				

*p < .01

**p < .001

Early onset and late onset of fetal growth retardation were defined in the following ways. Early onset consisted of sga (according to the Colorado Intrauterine Growth Chart) in the presence of smoking in pregnancy (greater than 15 cigarettes a day), viral infection, congenital anomalies, and maternal chronic disease (in our study only diabetes was noted in this category). Late onset of fetal growth retardation consisted of sga in the presence of maternal hypertension and/or pre-eclampsia. A third group of sga children (n=2) were defined as those with unknown etiologies. This group was made up of sga children who fit neither criteria for the early or late onset groups. Table 52 shows the characteristics of these three groups of sga children and Tables 53 through 56 portray the results.

TABLE 52. Characteristics of Children with Early and Late Onset of Delayed Fetal Growth.

Early Onset		Smking	Infection	Cong. Anomalies	Diabetes
n=4					
HEV	#1	X			
	#2	X		X	
	#3			X	
Registry	#4		X	X	
Late Onset		**Hypertension**		**Pre-eclampsia**	
n=3					
HEV	#1			X	
	#2			X	
Registry	#3	X		X	

As can be seen from Tables 53 through 56, none of the analyses are statistically significant. Only the perceptual performance scale of the MSCA approaches signficance (p=.072). Thus the data does not confirm the hypothesis that certain subgroups of sga children do poorer prognostically.

TABLE 53. Kruskal-Wallis One Way ANOVA on the MSCA

	Verb	Perc	Quant	GCI	Mem	Mot
Chi Square	1.36	5.25	2.78	1.14	1.89	1.89
Significance	.506	.072	.249	.566	.389	.39

TABLE 54. Kruskal-Wallis One Way ANOVA on the PIC-R Scales

PIC-R Scales	Chi Square	Significance
Adj	3.16	.206
Ach	3.43	.18
IS	2.0	.368
Dvl	3.16	.206
Som	2.57	.276
Dep	.96	.620
Fam	0.0	1.0
Dlq	3.43	.18
Wdl	1.84	.399
Anx	2.26	.323
Psy	.86	.651
Hpr	.86	.651
SSK	2.0	.368

TABLE 55. Kruskal-Wallis One Way ANOVA on the DOTS-R Dimensions

DOTS-R Scales	Chi Square	Significance
Act-General	1.5	.221
Act-Sleep	2.0	.157
App/Wdl	1.5	.221
Flex/Rig	1.5	.221
Mood	1.5	.221
Rhy-Sleep	.5	.480
Rhy-Eating	1.5	.221
Rhy-Dly Hab	1.5	.221
Task Orient	1.5	.221

TABLE 56. Kruskal-Wallis One Way ANOVA on the Bender Gestalt and Handicap

	Chi Square	Significance
Bender Gestalt	1.24	.539
Handicap	1.12	.572

H6: Presence of documented congenital viral infection will be associated with poorer prognosis.

Congenital viral infection was documented in only two subjects, both of which were Registry controls. Despite this low incidence, significant correlations at the .05 level of statistical significance were noted on two measures: the motor scale of the MSCA and degree of handicapping conditions. On both measures, presence of infection was associated with poorer outcome. These results can be viewed in Tables 57 through 60.

TABLE 57. Correlation Between Viral Infection and the MSCA

Verbal	Perceptual Performance	Quantitative	GCI	Memory	Motor
-.19	-.09	-.19	-.19	-.18	-.31**

**p < .005

TABLE 58. Correlation Between Viral Infection and the PIC-R Scales

Adj	Ach	IS	Dvl	Som	Dep	Fam	Dlq	Wdl	Anx	Psy	Hpr	SSK
-.05	.05	-.11	.10	-.20	-.15	-.06	-.23	-.15	-.10	.02	-.06	-.06

TABLE 59. Correlation Between Viral Infection and the DOTS-R Dimensions

Act-G	Act-S	App/Wdl	Flex/Rig	Mood	Rhy-S	Rhy-E	Rhy-D	H	Task
.26	-.10	.25	.22	.11	.01	-.01	.21		.07

TABLE 60. Correlation Between Viral Infection and the Bender Gestalt and Handicap

Bender Gestalt	Handicap
.14	.24*

*p < .05

Chapter Summary

This chapter has attempted to summarize the results of the research project. Initially, a description of the HEV group of children was delineated. Following this was an outline of the statistical procedures used in the analysis of the results. Lastly, each research hypothesis was discussed in turn with the applicable results.

CHAPTER V

Discussion and Research Implications

This chapter will discuss the results and implications of the research project. Concluding the chapter will be future directions to be taken by the research.

Discussion

Results from the research were both unexpected and expected. For instance, the failure to find statistically significant differences by group membership at the .05 level of significance while controlling for confounding variables was not anticipated. Other unexpected findings that were hypothesized about included a very low incidence of sex differences, absence of confirmed congenital viral infection in the HEV group, and the failure to find differential outcomes by various subgroups of sga children. Equally surprising was the statistically significant role chronic villitis and maternal hypertension had in predicting outcome.

Falling more in line with anticipated results are the statistically significant correlations of various pre-, peri-, and postnatal factors to outcome, including birth weight, maternal age, multiple gestation, ordinal position, smoking during pregnancy, maternal hypertension or pre-eclampsia, maternal diabetes, fetal distress, sga, viral infection, race, cesarean section, marital status, gravida, parity, parental education, and income level.

In order to best discuss the research findings, this section

will be organized much like the preceeding chapter where each hypothesis is stated and the results discussed.

H1: Those children with HEV affected placentas will do the poorest on outcome measures. The Registry control group will have lower scores than those children in the community control group but not as low as the children in the HEV group.

HEV does appear to be an important factor when examining outcomes for the children assessed within this study despite a failure to find statistically significant group differences on the various outcome measures. For example, higher incidences of both chronic villitis and maternal hypertension are found in the HEV group as can be seen from Table 4. A 43% vs. 22% incidence of chronic villitis is noted, while maternal hypertension occurs at the rate of 30% and 14% for the HEV and Registry groups respectively. Thus children in the HEV group have significantly ($p < .05$) increased incidences of these two conditions which are associated with poorer prognosis than children in either of the two control groups. However, regardless of group status, children with these conditions appear at risk for poorer functioning as assessed within this study.

The increased incidence of these two conditions in the HEV group suggests that somehow group membership and chronic villitis and maternal hypertension are inter-related. There are problems regarding the diagnosis of hypertension, to be discussed later, leading us to consider more heavily the relationship between the two placental conditions of chronic villitis and HEV. Precisely how these conditions might be associated cannot be sorted out in the

present study. We know neither the etiology of HEV nor chronic villitis, thus it is impossible to sort out which of the two may be the true predictor of poorer outcome or if some third factor may account for the lower scores noted in this study. Further investigations are called for in order to sort out which factor(s) contribute to poorer outcome, under which circumstances, and affecting which children.

We also note that this study found a lower incidence of chronic villitis in the HEV group than have prior studies (43% incidence in the present study vs. 60% in a prior study; Stevens and Sander; 1984). Incidence for the Registry control group was similar (22% in the present study vs. 20% in the prior study). It is noteworthy that the earlier study examined HEV affected placentas of both liveborn and stillborn infants whereas this author examined only data pertaining to liveborns. It may be that the difference in the 43% incidence and the 60% incidence of chronic villitis in the HEV group may be accounted for by the group of stillborns in the earlier study. This raises the issue regarding mortality and morbidity associated with chronic villitis.

In his examination of VUE, Russell (1980) notes that the severity of the villitis process correlates positively to both degree of perinatal mortality and IUGR. Mild villitis (defined as occassional to few lesions per full thickness section of placenta with no more than one focus of inflammation per low power field) was associated with a perinatal mortality rate of 16.9/1000 (seven of 415) whereas moderate villitis (frequent focal lesions and up to 25 percent involvement of the material studied) had a rate of 23.3/1000

(three of 129) and severe villitis (widespread and diffuse involvement of the placental villous tissue of over 25 percent, by the inflammatory process) had a rate of 129/1000 (four of 31). The perinatal mortality rate for severe villitis was significantly different from the first two. The mild, moderate, and severe villitis infants had birth weights for ga below the tenth percentile at 5.7%, 9.1% and 34.4% respectively, compared to the non-villitis control group of 3.5%.

The present study did not examine degree of chronic villitis. Thus it can only be hypothesized that the poorer function of the HEV group on some of the outcome measures may reflect a dose-response relationship regarding chronic villitis. This present study further leads us to expect milder forms and less frequent incidences of villitis in the Registry control group and more severe forms with greater rates of occurrence in the HEV group. Heightened incidences of IUGR and mortality would then be expected for the HEV group, along with possibly poorer prognosis on some of the outcome measures.

The three factor ANOVA notes statistically significant main effects for chronic villitis on the adjustment and delinquency scales of the PIC-R. An examination of Table 16 reveals the group by sex breakdown of mean scores. (Presence of chronic villitis could not be determined for the community control group since none of the placentas were examined. Thus the high score on the delinquency scale for the community controls cannot be explained by presence of chronic villitis since all were coded "no" on this variable.) The adjustment scale was designed as a screening device

to identify children with poor psychological adjustment. The delinquency scale was designed to measure delinquent tendencies and aid in identifying delinquent children and correlates most strongly with the adjustment scale (r=.53). For the HEV and Registry control groups, it appears that the inflammatory process that affects placental villi correlated with poorer outcome on these two scales of the PIC-R. To the extent that potential confounds have been measured adequately, we can make some casual inferences regarding the role of chronic villitis to pathology at five years of age. However, in the absence of random assignment in the research design, such inferences will remain at best, tenative. It is possible that these confounding variables are part of a biological process predisposing a subgroup of children to later problems. It is also possible that an unknown confounding variable(s) account for these significantly elevated scores.

Group effects are noted on two scales of the PIC-R: delinquency and hyperactivity, however due to the unbalanced nature of the design, the effects of chronic villitis (the first variable in the analysis) cannot be considered to be independent of group effects (the second variable in the design). The community control group (see Table 16) received the most pathologic scores on these two scales. The explanation for this is not readily apparent to this author. It may be that this reflects parental over-concern, particularly for female children, in these areas of personality. In the absence of pregnancy risk factors and birth complications for this group as a whole, it is also possible that (unsupportive) environmental influences might account for these elevated scores.

The literature on maternal hypertension strongly suggests this as a risk factor in pregnancy and outcome. It is noted as being associated with IUGR, increased rates of perinatal mortality and premature delivery, and later neurologic impairment (Ounsted, Moar, Good & Redman, 1980; Ounsted, Moar & Redman, 1980; Salonen & Heinonen, 1984; Silverstone, Trudinger, Lewis, Bulpitt, 1980). There may also be some variability in outcome depending on how and if the hypertension was treated during pregnancy, although conclusions vary on this issue. One theory pertaining to variability of hypertensive outcome suggests that maternal hypertension is an adaptive response which facilitates increased blood flow to the fetus. Treated hypertensive disease may then decrease blood flow and be associated with poorer outcome. Thus, this study may reflect the "protective" effects of maternal hypertension on certain measures where the presence of this condition is associated with improved outcome compared to the absence of this condition.

Socio-economic variables were found to correlate significantly to developmental outcome in follow up studies of these children with maternal hypertensive disease during pregnancy (Cockburn, Ounsted, Moar, Redman, 1982; Ounsted, Moar, Cockburn, Redman, 1984; Ounsted, Moar, Good & Redman, 1980). It may well be that certain (unmeasured) socio-economic variables and/or environmental factors functioned in the present study so as to heighten the development scores on the PIC-R for children without maternal hypertension. (This scale measures retarded development in motor coordination, poor school performance, an absence of any special skills or

talents, and limited motivation.)

The influence of (unmeasured) socio-economic and/or environmental factors may again be what is noted on the DOTS-R results where we see presence of hypertension in pregnancy associated with increased approach behavior across groups, while the presence of hypertension in the HEV group is associated with poorer functioning on the dimensions of mood, rhythmicity-sleep, rhythmicity-daily habits, and task orientation. The opposite pattern is noted for the Registry control group (i.e. presence of hypertension is associated with higher functioning on these same scales).

Perhaps we are seeing the effects of differing severities or treatments (including non-treatment) of maternal hypertension, where certain types of hypertension are systematically offset by an enhanced environment and/or maturational processes. Other types of maternal hypertension (i.e. treated, more severe, superimposed pre-eclampsia or maternal disease) may tend to be more numerous in the HEV group and/or more resistant to the ameliorating effects of maturation and/or a supportive environment.

It is interesting to note the higher proportion of abnormal MSCA and/or PIC-R scores associated with chronic villitis, maternal hypertension, or both in the HEV group compared to the Registry control group (65.4% and 34.6% respectively; see Table 40). Also noteworthy is the greater incidence of severe handicap for this group of children. Whether this points to differing severities of chronic villitis, different treatment types or superimposed conditions on maternal hypertension or other factors is unknown at

this time. It does appear that somehow this association for the HEV group is more pathologic than for the Registry control group.

H2: Male sex will be associated with poorer outcome.

Although we don't understand mechanisms behind the thesis of a male biological vulnerability, it has been acknowledged for some time. Various epidemiological studies have noted its existence. Yet this apparently fails to be substantiated in the present study and so an explanation is sought.

The male/female ratio in our study overall was disproportionate between the two sexes with 40% of the participants being male and 60% being female. The greatest inequity is noted in the HEV group as can be seen in Table 3. Within the HEV group, the present study notes a higher incidence among females than do prior investigatons which examined both liveborns and stillborns (70% female incidence in the present study vs. 57% previously, Stevens & Sander, 1984). It could be that females with HEV affected placentas are hardier than males and thus survive the neonatal period at increased rates, thus lending some credence to the thesis of a male biological vulnerability. Additionally, it could be that male HEV survivors come through the neonatal period and early childhood relatively more intact than their female counterparts, thus accounting for fewer and less severe rates of handicapping conditions. Unassessed environmental factors may somehow be influencing outcome as well. Another possible explanation is that a greater proportion of the nonrespondents, and particularly of the HEV nonrespondents, were male. These hypothesized male nonrespondents may have been systematically different than the

male respondents. Indeed, there is some evidence linking nonrespondents to more pathology than respondents. If these nonrespondents had been included in this study, perhaps sex differences may have emerged. The male/female ratio may have been more equal as well.

H3: Certain factors in the pre-, peri-, and/or postnatal environments will correlate to poorer prognosis.

Many of the correlations were as expected and in the anticipated direction. Of interest was the failure of certain factors to correlate significantly to any of the outcome measures. Falling in this category were two variables: gestational age and marital seperation at time of assessment. Regarding the former variable, it seems that a shorter gestation is less important than other conditions which may accompany it, such as lbw, sga, or maternal disease and other risk factors. When considering the latter variable of marital seperation, it must be remembered that the other three categories of marital status (married, single, divorced) did correlate significantly to at least one outcome measure. Why marital seperation fails to correlate significantly is not readily apparent to this author. Perhaps this "in between" stage of marital status is less impactful (either positively or negatively) than marriage at the one end of the continuum with its noted positive effects in some of the literature, and the stresses of divorce or singleness at the other end.

H4: Socio-economic variables will be positively correlated to outcome.

Not surprisingly, parental education correlated to more

outcome measures than income level. Maternal education in particular had the strongest positive association to all measured aspects of intelligence on the MSCA with the exception of the motor scale. Personality measures correlated much less often with these variables. Not surprisingly, the family relations scale of the PIC-R correlated significantly to all four socio-economic variables, with the strongest magnitude being income at time of assessment. Specifically, lower income categories were associated with greater family problems. This is in keeping with a body of literature which points to the stresses (i.e. of unemployment, depleted finances, alcoholism, physical illness, etc.) which accompany lower income levels. Maternal and paternal education correlated significantly to some aspects of rhythmicity and task orientation dimensions on the DOTS-R. An explanation for this is not obvious to this author.

H5: Presence of fetal growth retardation will be associated with lower scores. Additionally, early onset of delayed fetal growth will correlate to poorer outcome than will late onset of fetal growth retardation.

In a prior study, incidence of IUGR in HEV liveborns and stillborns was 33% (Stevens & Sander, 1984) compared to 15% in the present study examining only liveborns. Both studies used the same criteria (weight less than the tenth percentile for ga) and the same growth chart. Thus, it is likely that some of the other differences noted between the two studies (i.e. in the present study compared to the prior study, the HEV group noted an increased incidence of female subjects and a lower incidence of chronic villitis) may contribute to a lower incidence of IUGR than has been previously

found.

Significant correlations with the MSCA motor scale and degree of handicap are not surprising, and are in the expected directions. What seems unexpected to this author is the strong correlation with the psychosis scale of the PIC-R. This may suggest that IUGR is part of a biological process predisposing certain children towards this form of pathology, which the authors of the measure describe as assessing "acting out behaviors" at this particular level on the scale. How this risk factor may interact with environmental and familial risk factors cannot be sorted out in the present study.

Equally unexpected was the failure to find differences among certain subgroups of IUGR children. As is the case with many of the (unexpected) findings in this study, this author looks to environmental/caretaking factors for possible explanation.

H6: Presence of congenital viral infection will be associated with poorer prognosis.

This study found only two incidences of congenital viral infection; both of which involved Registry control children. In both instances, the infections were of the TORCH group. Significant correlations to the MSCA motor scale and degree of handicap are in keeping with the literature's range of clinical manifestations. Some of the more severe outcomes were noted in one of the children who had rubella in utero, including a profound hearing loss, heart defect, legal blindness in the left eye with a cataract and 20/80 vision in the right eye.

The absence of congential viral infection amongst HEV children is not altogether surprising since the prior investigation by

Stevens and Sander (1984) similarly revealed a small incidence. This author expects that were the study expanded, a small percentage of children with HEV affected placentas and congenital viral infection would be apparent, but perhaps a group size of 40 is too small to detect this subgroup of HEV children.

Despite the absence of congenital viral infection in the HEV group, an infectious association (this term is used loosely, including both a response to a viral agent or abnormal immune response, both of which are postulated mechanisms for chronic villitis) with HEV is still suspect due to the incidence of chronic villitis in a sizeable proportion of this group (43% in the present study and 60% in a prior study encompassing stillborns and liveborns). It may be that this infectious association constitutes a subgroup of the HEV population. Other subgroups within the HEV population are not known at this time.

Future Directions for Research

The direction that the research needs to take has largely been alluded to in earlier portions of the chapter. Nevertheless, it will be reiterated here.

It appears that the present project is not able to address four important areas, which if understood, would more clearly elucidate the etiology of HEV and prognosis for children with HEV of the placenta. First, the severity of chronic villitis needs to be assessed. This will further a response to the question regarding a dose-response relationship with chronic villitis to later outcome. Additionally, it might point to a higher incidence of more severe placental involvement in the HEV group in contrast to the Registry

control group. The grading of severity of chronic villitis should be made by a pathologist who is blind to the group status of the examined tissue. Thus there are implications for a collaborative effort among two or more pathologists in identifying presence of HEV and severity of chronic villitis.

The severity of HEV might also be examined to see if certain subgroups of children with differing severities of HEV correlate to later outcome. How this may interact with the extent and severity of chronic villitis would also be of interest.

A second area requiring further research centers upon maternal hypertension. Foremost would be the need to have a uniform method for diagnosing this condition. Additionally, treatment or non-treatment, and type of treatment should be measured. It may also prove helpful to assess concurrent problems such as superimposed pre-eclampsia or chronic maternal disease to see if these conditions interact with maternal hypertension and later prognosis.

Much of the literature review points to socio-economic and environmental factors as being significant correlates to outcome. Although this was found to be the case in the present study, what we failed to detect were significant group differences on these variables. Thus, this is an area requiring further investigation. It is this authors belief that an assessment of the quality and nature of the home and caretaking environments would yield useful information. Stability in the home, child-rearing attitudes, orientation to discipline, role definitions of family members, religious attitudes, current and past stresses, family cohesion, adaptibility, day care or school involvement, and community

involvement are among those aspects which, if measured, may lead to a fuller understanding of why some children have normal or better outcomes and some do not.

A final area for future investigation involves following a group of children over time and annually reassessing them. Ideally, the child and caretaking environment would be assessed within six to nine months after birth using multiple measures of infant development, health appraisal of mother and infant, infant temperament, and home environment. Then annually thereafter, these same children should be re-evaluated up through ten years of age as a minimum, to get a measure of changes over time. A more efficient way to do this of course would be to identify HEV children from birth through eight years of age (since HEV was discovered in 1977, the original children with the lesion would now be seven and eight) and to assess them using their age appropriate measures, followed by an annual reassessment for two more years. Thus, in three years time, we would have some longitudinal results using this sequential time series design. However, regardless of the method, a longitudinal study is essential in order to more fully comprehend the risk status for children with HEV of the placenta.

Conclusions

This study reveals that as a group, children with HEV affected placentas appear to be at greater risk for poorer prognosis on certain outcome measures at five years of age than children in either a Registry or community control group. This poorer outcome is statistically associated with increased incidences of those pregnancy and risk factors associated with poorer outcome as

assessed within the present study. Specifically, this study notes a 43% incidence of chronic villitis in the HEV group compared to 22% in the Registry control group and a 30% incidence compared to 14% for maternal hypertension in the HEV group and Registry control group respectively. Additionally, both chronic villitis and maternal hypertension are significantly associated with poorer functioning on measures of personality and temperament. A 65% and 35% incidence of abnormal scores on the MSCA and/or PIC-R for the HEV and Registry groups respectively are associated with these conditions.

Due to the non-random nature of the research design, causality of HEV, or its etiological function in chronic villitis, or the presence of a third etiological factor cannot be ascertained in the present study. This study notes that both chronic villitis and maternal hypertension are observed simultaneously with non-HEV children, so it appears that these conditions alone cannot explain HEV's etiology. It may be that the severity of involvement and/or interacting pregnancy, birth, or environmental factors are causally related to HEV. Although the mechanisms behind this are presently unknown, it is felt that the inter-relatedness of chronic villitis and HEV may contribute to poorer outcome for a subgroup of children.

It is apparent from the present study that many of the HEV children (35%) have normal outcomes as assessed at five years of age. Indeed, many children in both the HEV and Registry groups appear to be developing and functioning normally despite the presence of various pregnancy and birth complications. Further, it is noted that 25% of HEV children with chronic villitis and 16.7% of

Registry control children with chronic villitis have normal outcomes. The rates for normal outcomes in the face of maternal hypertension are slightly better for both groups, 44.4% and 25% for the HEV and Registry groups respectively. This would not be expected from the premises embodied with the continuum of reproductive casualty. Thus it appears that a linear relationship between reproductive casualty and sequelae is unsupported by the present research.

The viability of a continuum of caretaking casualty to explain enhanced outcome by certain children across groups must be explored further. This study suggests that higher levels of parental education and income do benefit the child. Maternal education held the strongest correlation to the most outcome scales (9), followed by paternal education (7), income level at time of assessment (4), and lastly, income at birth (2). However, the transactional process of child and environment influencing each other over time cannot be addressed herein. Therefore, the author feels there is insufficient data in the present study to assess to the ameliorating influence of a positive caretaking environment as posited by Sameroff and Chandler.

An infectious association does seem likely for at least a subgroup of HEV children, if one accepts the premise that VUE is of infectious association (the term infectious association is used loosely here to encompass both a postulated viral infection or an abnormal immune response). It is neither confirming nor disconfirming that this study notes an absence of documented congenital viral infection among the HEV children, due to its small

incidence in prior studies. It seems that what is needed to confirm a viral association for children with HEV and simultaneous chronic villitis, is to gain a fuller understanding of the etiology of chronic villitis. As was noted in the literature review, there is some consensus among pathologists on this issue, but confirmation is still lacking.

It does not appear that children with HEV affected placentas are a homogenous group. Precisely what delineates one subgroup from another is only beginning to be understood. It does appear that HEV children with simultaneous chronic villitis and/or maternal hypertension appear to fair poorer on personality and temperament measures at five year follow up than their counterparts without these conditions. Exactly what the mechanisms are remain unknown. Additionally puzzling is the higher proportion of abnormal scores in the HEV group compared to the Registry control group where associations of chronic villitis and/or maternal hypertension exist. Whether these outcomes change over time and how outcome interacts with environmental factors is similarly unknown. Thus, like so many other research projects conclude, it seems that the gulf in our knowledge regarding this heterogeneous group of children is great and what is known seems so small. However, if this can serve as a stepping stone for later investigations, then its purposes will have been well served.

GLOSSARY

Appropriate for gestational age (aga)-a term designating infants who are adequately grown for their gestational age according to various growth charts; typically denoting a weight greater than the tenth percentile.

Asphyxia (or hypoxia or anoxia)-a reduction in oxygen level below the requirements of the organism, requiring intervention. There are many methodological differences across studies, including definitions of asphyxia by Apgar scores, time until the infant can breathe unassisted, and measuring oxygen level in the blood.

Chronic villitis-a chronic inflammation within placental villi due to a variety of infectious agents. Chronic villitis may be of known and unknown etiologies. In the latter instance, it is referred to as villitis of unknown etiology or VUE. A 60% incidence of chronic villitis occurs in HEV affected placentas.

Congenital anomalies-any abnormality including malformations present at or detectable immediately after birth, resulting from perinatal environmental insults (e.g. infectious agents or teratogens).

Hemorrhagic endovasculitis (HEV)-damage with inflammation of the fetal placental blood vessel with resulting blood loss and destruction of fetal red blood cells.

Inclusion bodies-a microscopic term wherein the nucleus of a cell is observed to have something in its center, most often clumped

chromatin, or genetic material, which is indicative of viral damage.

Low birth weight (lbw)-infants whose weight at time of birth is less than 2500 grams (five and one half pounds).

Ponderal index (PI)-as used in this study, a means for classifying the fetally malnourished infant that is underweight for its length by gestational age.

Prematurity-gestation of less than 37 completed weeks. In earlier studies this may have been defined by a low birth weight.

Serial ultrasonic cephalometry-as used in this study, it is a method for detecting timing or onset of fetal growth retardation.

Small for gestational age (sga)-various criteria are used to designate this group of premature and fullterm infants who are inadequately grown for their gestational age. Other terms are used interchangeably to denote this population, including small for dates (sfd), light for dates, intrauterine growth retardation (IUGR), fetally malnourished, growth retarded, and low ponderal index (low PI) babies.

TORCHES group-a group of infectious agents including toxoplasmosis, rubella, cytomegalovirus (CMV), herpes, and other infectious agents. This group is implicated in the etiology of chronic villitis and therefore HEV.

Very small for date (vsfd)-used in studies employing a stricter criteria to denote this subgroup of sga children. It is often used in contrast to a group of sga infants.

APPENDIX A

The Michigan Placental Tissue Registry

The Michigan Placental Tissue Registry is a diagnostic referral center which receives placental specimens associated with any abnormality in pregnancy and is available to physicians across the state. During the time period encompassed by this study, the Registry was supported by grants and was therefore a free service to the public. Placentas referred are those associated with any problem concerning pregnancy, delivery, or abnormalities of the infant, including maternal infection, difficult labor or delivery, malformed or stillborn infant, or abnormal placenta.

APPENDIX B

The Colorado Intrauterine Growth Chart

The Colorado intrauterine growth chart is described in the 1963 article by Lubchenco, Hansman, Dressler, and Boyd. The sample included caucasian and Spanish-American (30% of sample) liveborns with gestations ranging from 24 to 42 weeks. Only certain gestations were included in the normative data. The weekly intervals for gestational age were figured from mid-week to mid-week on the curve. Various socio-economic levels were represented in the sample, including the medically indigent. Twenty six infants with gross pathology (hydrocephaly), maternal diabetes, and other conditions directly affecting birth weight were also included in the sample. Seperate curves for each sex plus a combined curve are provided. There are percentile values of ten, 25, 50, 75 and 90.

APPENDIX C

Maternal and Child Questionnaires

Maternal Survey

1. Have you ever been told by a doctor that you had a heart murmur or anything wrong with your heart?
2. Has a doctor ever told you that you had diabetes or sugar in your urine?
3. Have you ever had thyroid trouble?
4. Have you ever had any trouble with your kidneys or bladder?
5. Have you ever had any allergies or allergic conditions?

   If yes:

   a. Do you know what you are allergic to? What is it?

   b. What type of a reaction did you have?

      hayfever asthma eczema hives

6. Have you ever had a reaction to any drugs or medicines such as penicillin, sulfa, etc.?
7. Have you ever had a skin growth or any other kind of skin trouble?
8. Have you ever had any pain or swelling in your joints?
9. Have you ever had phlebitis or a blood clot?
10. Have you ever had a convulsion or a seizure?
11. Have you ever had anemia?
12. Have you ever had any trouble with your uterus or ovaries?
13. Have you ever had any trouble with your periods?
14. Has a doctor ever told you that you had hepatitis or any other

liver trouble?

15. OBSTETRICAL HISTORY

We would like to record some information about pregnancies for each of the women in the study. We are interested in all pregnancies, including miscarriages, abortions, stillbirths and of course live births.

I would like to begin with your first pregnancy and go through all of your other pregnanies in order of occurrence.

OBSTETRICAL HISTORY FLOW SHEET

	Status		Your	Pat.	Pre & Post	Live Births				Other	
No.	LB	Oth	Age	Age	Complications	name	sex	date	wt	month	cause

Summary: Gravida

Para

Abortus

Induced

Stills

Neos

Living

Other Deaths

Comments

16. Have you ever had any of the following? during pregnancy? (#/month)

high blood pressure

sugar in urine

urinary tract infection

herpes

measles

rubella (G. Measles)

chicken pox

CMV (cytomegalovirus)

17. During any of your pregnancies, did you have any of the following? (#/month)

toxemia or pre-eclampsia

bleeding

cramping

fever

flu or cold (that kept you in bed)

physical injury

eclamptic seizures

hepatitis

other

18. During any of your pregnancies did you take:

anything for headache, pain or fever?

any prescribed medicines?

anything for nausea?

any other medicines?

19. During any of your pregnancies did you use any of the following:

cigarettes

alcohol

caffeine

marijuana

other drugs (specify)

20. During any of your pregnancies, did you gain:

more than 30 lbs.

less than 20 lbs.

21. DEMOGRAPHIC INFORMATION

date of birth: race: income:

last grade of school completed: previous income:

age at first intercourse: #SP: Marital Status:

occupation: currently employed:

during pregnancy:

3 years prior:

where did you live during the pregnancy:

urban suburban rural

3 years prior to the pregnancy:

urban suburban rural

22. Have you ever been exposed to any irritating gas or fumes?

What kind?

Did this cause you to be sick?

Did you have to miss work?

23. Have you ever been hospitalized for other than pregnancy?

24. Have you ever had surgery other than above?

25. Do you take any medicines now?

How long have you been taking this?

26. Is there anything important about your health which we haven't discussed?

27. FATHER DEMOGRAPHIC INFORMATION

date of birth: race: income:

last grade of school completed? previous income:

occupation: currently employed:

during pregnancy:

3 years prior:

where did he live during your pregnancy?

urban suburban rural

3 years prior?

urban suburban rural

28. Has father had still born, small for dates or abnormal children in a previous or subsequent marriage or relationship?

29. Has father ever been exposed to any irritating gas or fumes?

What kind?

Did this cause him to be sick?

Did he have to miss work?

30. Did father take any medicines or drugs in the 3 years prior to the pregnancy?

31. Has father ever been hospitalized?

32. Has he ever had surgery other than above?

33. During your pregnancy and the 3 years prior, was the father frequently away from home overnight?

34. Has the father ever had any of the following?

hepatitis

herpes

CMV (cytomegalovirus)

rubella

measles

other infection

35. Is there anything else about his health or lifestyle that you think is important?

36. Has your mother or any of your siblings had a history of pregnancy problems?

37. Has your mother or any of your siblings had any children with handicaps, chronic illnesses or learning disabilities?

38. Have you or your parents ever had any mental or emotional problems?

39. Has _____'s father or his parents ever had any mental or emotional problems?

person	age	problem	duration	outcome

Child's Survey

1. How is _____'s health now?
2. Has s/he ever had any trouble with his/her digestive system?
3. Has s/he ever had any trouble with his/her kidneys or bladder?
4. Can _____ usually sleep through the night without wetting the bed?
5. Has s/he had any trouble breathing?
6. Has s/he ever had a convulsion or a seizure?

   Did s/he have a high fever at the time?
7. Has s/he had any pain or swelling in his/her joints?
8. Has s/he ever had a staring spell?
9. Has s/he ever lost consciousness or fainted?
10. Has s/he ever had nervous twitches or tics?
11. Has s/he ever had any skin trouble?
12. Has s/he ever had any trouble hearing or other ear problems?
13. Has s/he ever had any trouble seeing?

    Wear glasses?

    Other eye problems?
14. Has s/he ever had any problems with bleeding or bruising easily?
15. Has s/he ever had any allergies?
16. Is_____ taking any medicine now?

    What is it?

    Reason:

    How long has s/he been taking this?
17. Has s/he ever had any surgery?

    age

reason

outcome

18. Has s/he ever been in the hospital (other than the times already mentioned)?

age

reason

outcome

The following questions pertain to the time around _____'s birth.

19. How long were you in labor with _____?

20. Was his/her delivery normal or were there complications?

21. Did you have an anesthetic?

Do you know what it was?

22. Did the doctor say anything about _____'s health at the time s/he was born?

23. Did s/he receive any special care at the hospital (oxygen, fluids)?

24. Did s/he go home from the hospital at the same time as you?

25. Was _____ breast or bottle fed?

The following questions are about _____'s general development. Compared to your other children or other children you know of, would you say s/he did the following things sooner, later, or about the same time as the others.

26. Sat up without support?

27. Started to crawl?

28. Walked without holding on to anything?

29. Cut first tooth?

30. Said first word?

Used 2-3 words together?

Used whole sentences?

31. Has s/he had any problems with his/her speech?

32. Please look at this list and check any of the activities which bother you about _____?

fussiness	doesn't pay attention
picky eater	accident prone
won't mind	nightmares
jealousy	too active
holds breath	eats paint or dirt
bad temper	hard to get to bed
slow to learn	very shy
unusual fears	difficulty relating to other children

33. Is _____ more or less difficult to raise than your other children or other children you know?

34. Has s/he ever been evaluated or treated for any mental or emotional problems?

age

problem

present status

35. Has s/he ever been seperated from one or both parents for 7 days or more (hospitalization of parent or child, marital sep.)?

36. Has s/he ever had any serious accidents (burns, cuts, poisoning, broken bones)?

37. Has s/he ever had any of the following?

german measles	hepatitis

measles chicken pox

cytomegalovirus herpes

any other viral infection

38. Does _____ presently, or did s/he previously attend:

day care

preschool

other (home care situation)

kindergarten

Hours per week

Began at age:

39. Is there anything else significant about his/her health which we haven't talked about?

Additional comments

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