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NEUROPSYCHOLOGICAL DEFICITS IN PEDIATRIC NEUROLOGICAL DISORDERS

by

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NEUROPSIGOLOGIESE TEKORTE IN

PEDIATRIES NEUROLOGIESE AFWYKINGS

deur

ROSANDRA DAWN CHAPMAN

OPSOMMING

Die doel van hierdie studie was om 'n ondersoek te loods na neuropsigologiese tekorte in kinders met pediatries-neurologiese siektetoestande. Vir die doeleindes van hierdie studie is die pediatries-neurologiese sindrome verdeel in die aandagsgebrek-hiperaktiwiteitsversteuring, aandagsgebrekversteuring, Tourette se sindroom en die gesinslede van kinders wat aan die wiegiedoodsindroom oorlede is.

Die rede vir hierdie ondersoek is dat daar tans in die sielkunde en die pediatrie verwarring is oor die spesifieke aard, oorsaaklikheid en interverwantskappe tussen die verskillende toestande hierbo genoem. Waar sommige outeurs meen dat Tourette se sindroom die oorkoepelende neuropsigologiese disfunksionele sindroom is, meen ander weer dat daar 'n sentrale neuropsigologiese disfunksionele patroon bestaan wat afhangende van sekere ontwikkelingsgebeure uitmond in die aandagsgebrek-hiperaktiwiteitsversteuring, aandagsgebrekversteuring, Tourette se sindroom en die wiegiedoodsindroom.

'n Komplekse model van neuropsigologiese funksie en disfunksie is ontwikkel om verskille en ooreenkomste tussen hierdie toestande te beskryf.

Om die lewensvatbaarheid van hierdie model te toets, is vier eksperimentele groepe en 'n kontrolegroep geselekteer. Die eksperimentele groepe was kinders met die aandagsgebrek-hiperaktiwiteitsversteuring, kinders met 'n aandagsgebreksversteuring, kinders met Tourette se sindroom en die bloedverwante van kinders wat aan die wiegiedoodsindroom gesterf het. Hulle is vergelyk met 'n kontrolegroep en met mekaar ten opsigte van 'n reeks kinder-neuropsigologiese toetse.

Die gegewens wat so bekom is, het aangedui dat daar wel betekenisvolle verskille tussen hierdie groepe onderling en met die kontrolegroep bestaan. Al die groepe het neuropsigologies slegter gefunksioneer as die kontrolegroep. Van besonder belang is dat die gesinslede van die sogenaamde wiegiedood-kinders die grootste disfunksionaliteit in hulle neuropsigologiese funksionering vertoon het. Daar was geen aanduidings gevind dat Tourette se sindroom enigsins 'n oorkoepelende sindroom is nie, en blyk dit dat hierdie toestand slegs een van die neuropsigologies-disfunksionele toestande beslaan.

CONTENTS

CHAPTER ONE

INTRODUCTION

1.1   Introduction

Although neuropsychological dysfunctions are the most common handicapping condition of childhood, with an estimated incidence of 15% or greater, (Pennington & Smith, 1988) relatively little is known about the etiology of the various disorders. The large majority of neuropsychologically handicapped children seen clinically cannot be clearly assigned an etiology, even when they receive an extensive interdisciplinary evaluation. In the absence on a clear understanding of etiology, it is difficult to approach early detection, prevention, intervention, or prognosis in a rational way. It is increasingly recognised that neuropsychological disorders are heterogeneous both in their etiology and in their clinical presentation and course (Benton & Pearl, 1978; Rie & Rie, 1980). However, there appear to be basic paediatric neuropsychological dysfunctions with different manifestations, such as Sudden Infant Death Syndrome, Tourette's Syndrome, Attention Deficit Hyperactivity Disorder, and Attention Deficit Disorder.

Sudden Infant Death Syndrome and Tourette's Syndrome are both controversial as regards definition, etiology and explanatory mechanisms. Upon further investigation however, it appears that physically, both these disorders are as a result of a neurological deficiency. However, there is another group of "soft" neurological sign-oriented conditions namely Attention Deficit Disorder and Attention Deficit Hyperactivity Disorder. Attention Deficit Hyperactivity Disorder has been controversial since it was first described in the 1930s. A current controversy is whether Attention Deficit Hyperactivity Disorder is a learning disability or a related disorder (Murphy & Hicks-Stewart, 1991). It could be postulated that these conditions show so much overlap that they form sub-groups of the same condition.

Contrary to Comings and Comings (1987a) proposal that the Tourette's Syndrome gene is one of the causes of Attention Deficit Disorder and that Attention Deficit Disorder is one of the pleiotropic effects of the Tourette's Syndrome gene, this study was undertaken to investigate whether Attention Deficit Disorder, Attention Deficit Hyperactivity Disorder Tourette's Syndrome, and the symptoms manifested by siblings of Sudden Infant Death Syndrome victims are not manifestations of a neurodevelopmental deficit that manifests in different ways. It was hypothesized that the above-mentioned disorders were all caused by a pervasive neurological deficit or disorder. Hyperactivity appears to be a common symptom in the above- mentioned disorders, as well as other Specific Developmental Disorders, and it is suggested that the gene responsible for the facilitation of the inhibition and arousal of sensory and

motor activity, is the cause of the disorders that are under investigation, and that these disorders are the pleiotropic effects of this gene.

As the etiology of Sudden Infant Death Syndrome, according to prevailing views is unknown, the disorder is difficult to treat because it is difficult to explain. The etiology of Tourette's Syndrome is also unknown, and therefore a disorder which specialists have difficulty treating, although some researchers have strong opinions about the origins and treatment of the disorder (Comings, 1987). Without a known cause or confirmatory neurologic/biochemical correlate, diagnosis of Tourette's Syndrome is based on observable clinical criteria. Consequently, clear descriptions of features that characterise the syndrome are vital to guide clinicians. Unfortunately, many Tourette's Syndrome criteria have proven to be inaccurate, which has necessitated repeated changes to the diagnostic criteria (Gedye, 1991). The same situation applies to Sudden Infant Death syndrome. Despite intensive research, the precise etiology and pathophysiological mechanisms still remain unknown (Beckwith, 1973). Results from the involvement of investigators with many diverse backgrounds, resulted in a large number of theories, many of which were subsequently discarded (Valdes-Dapena, 1988). This disorder also relies for diagnosis on observable clinical criteria. Therefore these disorders appear to be controversial in many areas.

Attention Deficit Hyperactivity Disorder has been controversial since it was first described in the medical literature in the 1930's. The research on Attention Deficit Disorder and Attention Deficit Hyperactivity Disorder reveals much uncertainty, but also a degree of understanding of the complexity of these two diagnostic categories. At present, it is generally accepted that these labels refer to heterogeneous disorders with unknown and mixed etiology, a poorly documented developmental course, and prognoses that may be as variable as the other characteristics (Rutter & Garmezy, 1983). There is considerable research in these areas but the definitional problems have resulted in a body of work that is inconsistent, contradictory, and inconclusive (Rutter, 1983).

However, Attention Deficit Hyperactivity Disorder has been subject to many reconceptualizations, redefinitions, and renamings. From its origins as minimal brain damage, through hyperkinesis, to attention deficit disorder with hyperactivity, little has remained constant in our understanding of the disorder (Lahey, Pelham, et al, 1988). Attention deficit disorders are associated with a variety of other childhood psychiatric problems, and numerous psychiatric conditions can present as attention difficulties. Co-morbidity has become an important area of research in recent years, as studies reveal that high percentages of children with Attention Deficit Disorder/Attention Deficit Hyperactivity Disorder also suffer from other disturbances.

✻ Few children present with pure symptoms of Attention Deficit Hyperactivity Disorder. Most have some

other problem, including learning disabilities, oppositional defiant behaviour, mood disorders (particularly depression), anxiety disorders, and among adolescents and young adults, substance abuse and personality disorders. In very young children, it is possible to mistake developmental delay and mental retardation for the signs of Attention Deficit Disorder/Attention Deficit Hyperactivity Disorder. In addition to the externalizing disorders, such as lying, stealing, fighting, many children with Attention Deficit Disorder/Attention Deficit Hyperactivity Disorder also exhibit symptoms of internalizing problems, including depression, bipolar illness, and anxiety. Rarely, a child may present with Tourette's Syndrome, obsessive compulsive disorder, or atypical thought processes.

It would appear that these conditions all form part of a single neuropsychological deficit or illness, which is important to investigate as the possibility that the overlap of these areas would be more significant than the differences, thereby suggesting that they should be treated as an entity with different outcomes based on either congenital or post-natal occurrences or events. However, before this can be undertaken, it would be important to pay some attention to the differential conditions of Sudden Infant Death Syndrome, Tourette's Syndrome, Attention Deficit Disorder, and Attention Deficit Hyperactivity Disorder in more detail.

1.2   Sudden Infant Death Syndrome

One of the most vexing problems in childhood mortality is the condition of Sudden Infant Death Syndrome. The term Sudden Infant Death Syndrome is used when no perceptible condition or diagnosable ailment can be identified. The use of the term "syndrome" in identifying the cause of death is conjectural, or at least premature, because no constellation of underlying disease factors has yet been found (Burns & Lipsitt, 1991). Numerous hypotheses about the origin of Sudden Infant Death Syndrome have been proposed. A review of research on Sudden Infant Death Syndrome over the last 20 years indicates that Sudden Infant Death Syndrome research has followed a similar pattern to other complex physiological or medical problems (Valdes-Dapena, 1978).

Most of these hypotheses have been discarded, and research has been directed towards dysfunctioning in more subtle areas such as neurophysiological mechanisms (Hoppenbrouwers and Hodgman, 1982; Valdes-Dapena, 1978; Kinney and Filiano, 1988). One of the leading hypotheses in Sudden Infant Death Syndrome research is that Sudden Infant Death Syndrome is caused by a subtle defect in brainstem neural circuits which control respiration and/or cardiac stability during sleep. The unique age distribution, with a peak period between 2-4 months, and the risk factors of prematurity and low birth weight is indicative that maturational factors are involved (Kinney and Filiano, 1988).

The brainstem centres that control respiration are very close to structures that control other body functions, and so any fault impairing the respiratory control mechanisms might also possibly affect those other functions (Schwartz, 1987). Non-respiratory impairments are observed in some babies who succumb to Sudden Infant Death Syndrome. These impairments include abnormalities in temperature regulation, feeding, and neurological reflexes. These abnormalities are often evident soon after birth. However, not much investigation has been done in correlating the various non-respiratory findings in Sudden Infant Death Syndrome infants with specific lesions of the brain (Naeye, 1980).

It is only recently that the condition has been recognized as a specific clinicopathological entity. As the majority of these deaths are accompanied by only trivial anatomic alterations, as plethora of hypotheses have been put forward to fill the factual void as the specific cause of death (Naeye, 1980). Many researchers and clinicians with "theories in search of diseases" have applied these to Sudden Infant Death Syndrome, with results that have varied from stimulating productive research on the one hand to the production of tragic guilt reactions on the part of families of victims on the other (Valdes-Dapena, 1988). Of the little that is known, there appears to be consensus that Sudden Infant Death Syndrome is caused multifactorially and that different mechanisms and causes are involved. This does not mean, however, that they are all equally important. Furthermore, it is possible that the proposed hypotheses account for a small number of Sudden Infant Death Syndrome cases and that most Sudden Infant Death Syndrome deaths are the result of a few critical mechanisms (Beckwith, 1973).

Sudden Infant Death Research has shown that no single mechanism explains all sudden infant deaths. However, to account for the consistent age distribution of Sudden Infant Death Syndrome, there may be a critical biochemical or molecular event in central nervous system development which occurs or peaks at 2-4 months and which involves a final common pathway in neuronal energy metabolism or neurotransmission upon which multiple insults act to produce sudden death (Howat, Bennett, Variend et al, 1985). If such an age-dependent final common pathway could be found, the relationship of diverse factors associated with Sudden Infant Death Syndrome eg. maternal smoking, maternal drug abuse, elevated fetal haemoglobin, (Guilian, Gilbert & Moss, 1987), brainstem gliosis, and increased dendritic spine density, may become clear (Kinney & Filiano, 1988). Valdes-Dapena (1988) states that the unique curve for their ages at death is independent of all other risk factors suggesting that, in most cases, there is probably an important underlying mechanism involving growth and development. It would thus appear that Sudden Infant Death Syndrome has a neurodevelopmental origin.

In the last few years research has shed some light on various epidemiologic aspects of the problem, on pathologic anatomy and on clinical issues such as the relative importance of spontaneous, prolonged, idiopathic apnea. Some Sudden Infant Death Syndrome victims showed evidence of neonatal brain

dysfunction, including abnormalities in respiration, feeding, and temperature regulation and have been shown to have pathologic abnormalities consistent with chronic hypoxia (Kelly & Shannon, 1982). Once again, however, the research appears to be inconclusive, leaving many unanswered questions.

Many factors are unique to Sudden Infant Death Syndrome: Age Of death, association with sleep, and increased risk for the second born. The proposed and possible cause and core deficit consists of mild hypoxia sustained during pre- and post-natal life, for which most infants successfully compensate. However, changes between one and three months of age in development and integration of the central nervous system gives rise to increased vulnerability to endogenous and exogenous deleterious influences during this period. Although the etiology of the core deficit is unknown, many factors can cause a mild hypoxia (Naeye, 1980).

Sudden Infant Death Syndrome is not considered to be genetically determined (Kelly, Twanmoh, & Shannon, 1982). However, recent data indicates that the incidence of Sudden Infant Death Syndrome in the families of infants who died of Sudden Infant Death Syndrome was increased (Irgens, Skjaerven, Peterson, 1984). Examination of Sudden Infant Death Syndrome infants has found abnormal neurologic results with findings similar to those of infants who were resuscitated quickly enough after a Sudden Infant Death Syndrome apneic episode, indicating expressions of intrinsic central nervous system abnormalities. Subsequent siblings have been shown to be at high risk for Sudden Infant Death Syndrome. Investigators have found abnormalities in breathing patterns and the respiratory control system resulting in apneic episodes (Valdes-Dapena, 1988). However, it is possible that a physiologic or pathologic abnormality in the mother could result in a pathologic condition in the brainstem, ultimately resulting in later neurodevelopmental abnormalities (Korobkin and Guilleminault, 1979).

In addition, some Sudden Infant Death Syndrome deaths occur among newborns and comprise as much as 10% of all neonatal mortality. Paediatric pathologists have demonstrated a high occurrence of dysmorphic, dysplastic and minor anomalous lesions in these children. These observations suggest that the former have experienced adverse influences prenatally which may make them particularly vulnerable to post-natal challenges (Valdes-Dapena,1988). Pathologic investigation of the infant who dies suddenly and unexpectedly is of utmost importance in order to :-

-        establish a diagnosis of Sudden Infant Death Syndrome,
-        assist in defining mechanisms of death in these situations,
-        and ascertain whether other factors, some of which are genetic, are present (Krous, 1988).

In Sudden Infant Death Syndrome, the necropsy yields the positive findings of intrathoracic petechiae

5

in a significant percentage of cases (Krous,1988). It is postulated that these haemorrhages are a significant indication of terminal upper airway obstruction in Sudden Infant Death Syndrome which may be caused by a disordered neuroregulatory control of respiration during sleep, by the brainstem (Krous, 1988). Evidence of hypoxia in the tissue of organs of children who have died from Sudden Infant Death Syndrome indicates that Sudden Infant Death Syndrome infants may have experienced prolonged or recurrent apneas (Krous, 1988). Whether due to dysmaturity or injury, it may be assumed that functional abnormalities would not be confined to respiration, as the brainstem areas that control respiration are not totally separated from other vital centres (Naeye, Ladis, Drage, 1976).

Families who have experienced a Sudden Infant Death Syndrome death are faced with the possibility of subsequent siblings being at increased risk of dying from Sudden Infant Death Syndrome (Irgens, Skjaeven, and Peterson, 1984). There is little consensus on the risks faced by subsequent siblings. While they may not manifest an increased risk for Sudden Infant Death Syndrome, they may show certain neurodevelopmental abnormalities (Van der Hal, Rodriquez, Sargent, Platzker and Keens, 1985), possibly suggesting a mechanism present in Sudden Infant Death Syndrome infants as well as their siblings, where the mechanism was more intense and lethal in the Sudden Infant Death Syndrome children specifically. An overview of the literature suggests that the proposed mechanism might include respiratory failure, decreased voluntary arousal during sleep and minor neurological anomalies.

The respiratory system of infants is immature and rapidly changing. Respiratory pauses during sleep up to 15 seconds in duration are common in normal infants and do not indicate any increased risk for Sudden Infant Death Syndrome. Therefore, it may not be so important how many pauses an infant has, as to how successfully he is able to terminate a respiratory pause and resume normal breathing. Arousal from sleep is a significant defence mechanism of the respiratory system for the cessation of apnea. Failure to arouse to an apneic or hypoxic episode during sleep may result in death of the infant if he cannot recommence normal breathing.

Harper, Hoppenbrouwers and associates (1978) undertook a series of studies in which they demonstrated that subsequent siblings of Sudden Infant Death Syndrome victims have decreased voluntary arousals during sleep. This supports the hypothesis that the failure to arouse in response to a respiratory pause or potentially dangerous hypoxic episode may prevent the infant from extricating himself from this episode, resulting in death. If, during sleep, an infant becomes hypoxic, an instinctive response is to arouse (Van der Hal, Rodriques, Sargent, Platzker, and Keens, 1985). As early as 1908, Tredgold postulated that hyperactive behaviour followed minimal brain injury, namely that caused by hypoxia. Towbin (1971) states that the fetus and newborn often incur hypoxic lesions which result in minor cerebral dysfunction which manifests as behaviourial disorders often accompanied by learning defects,

reading inability, attention deficit disorders, hyperactivity, and motor disturbances, described as extreme clumsiness, or atypical neurologic findings and electroencephalographic abnormalities. There is a wide belief that complications of pregnancy and birth, such as anoxia, can be associated with impaired development, cognitive deficits and behaviourial problems (Kelly & Shannon, 1982). However, the specific nature and cause of this condition continues to elude both scientists and practitioners.

As seen from the above, extensive research has been undertaken in a vigorous effort to identify the cause of Sudden Infant Death Syndrome and the infants at increased risk for it, However, while the knowledge about this syndrome has increased, the causes of this condition or the means for prevention, are still unknown. As no physiological data were initially available, epidemiological and pathological findings constituted the basis for several hypotheses. However, they were not found to be valid. Thus no one single mechanism can be identified as the cause of death and these mechanisms are thought to be multifactorial (Hunt and Brouillete, 1987). Current data support a complex model, characterised by interactions at many levels of the neuraxis, between the organic structure and the environment and including both pre- and post-natal life (Hoppenbrouwers and Hodgman, 1982).

It appears from data obtained in a study completed in 1991 in which siblings of Sudden Infant Death Syndrome were investigated regarding their neurodevelopmental characteristics, that this sub-group manifest a significant number of symptoms that are found in children suffering from Attention Deficit Hyperactivity Disorder (Chapman, 1991). There is therefore the distinct possibility that a sub-category of Attention Deficit Hyperactivity Disorder children is comprised of Sudden Infant Death Syndrome siblings.

1.3   Tourette's Syndrome

The pathophysiology of tics and specifically Tourette's Syndrome remain a mystery. There is also much controversy regarding the symptoms which should be included in a diagnosis of Tourette's Syndrome. The Yale Group consisting of D. Pauls, D. Cohen, J. Leckman and K. Towbin among others, postulate that Tourette's Syndrome be diagnosed according to the requirements of the DSM-111-R. However, Comings and Comings of the Duarte Group claim that not only obsessive-compulsive disorder, attention-deficit disorder, and learning disorders but conduct disorders, phobias, panic anxiety, schizoid behaviours, depression, manic depression, and sleep problems are all part of the Tourette's Syndrome spectrum and represent variant expressions of a Tourette's Syndrome gene (Comings & Comings, 1987a, 1987b, 1987c, 1987d, 1987e, 1987f).

There have been no studies that have demonstrated the existence of a gene for Tourette's Syndrome

either by the elucidation of linkage to a known genetic marker or by the identification of an abnormal protein or gene product (Pauls, Cohen et al, 1988).

Lang (1992) emphasized the clinical heterogeneity of Tourette's Syndrome which covers a broad spectrum of tic severity as well as behaviourial disturbances. A developmental history of hyperactivity has been reported in more than half of Tourette's Syndrome cases (Shapiro & Shapiro, 1978). Clinical criteria for the diagnosis of Tourette's Syndrome are defined operationally in the DSM-111-R and include; (1) the presence of multiple motor tics, (2) the presence of 1 or more vocal tics, (3) age at onset before age 21 years, and (4) duration of more than 1 year. However, despite the formulation of these criteria, Tourette's Syndrome is clearly a disorder that is clinically heterogeneous (Robertson, 1988), a problem that has greatly hampered research efforts to identify causal biochemical variables and has led to difficulties in interpreting epidemiologic, genetic, and therapeutic studies. The clinical manifestations of Tourette's Syndrome can best be viewed along a continuum that includes both motor and behaviourial features (Lang, 1992).

Many clinicians consider Tourette's Syndrome to be a rare, severe and disabling condition with bizarre symptoms and an unknown etiology. In recent years, concepts regarding Tourette's Syndrome and related disorders have undergone dramatic changes (Kurlan, 1989). Recent genetic studies indicate that Chronic Multiple Tic Disorder and Tourette's Syndrome are transmitted as hereditary traits in the same families and that Chronic Tic Disorder seems to be a mild form of Tourette's Syndrome (Golden, 1978: Pauls, Cohen, Heimburch et al, 1981). Although tic severity is known to wax and wane throughout the course of the illness, Tourette's Syndrome has long been considered to be a severe and disabling condition (Torup, 1972). However, Caine et al, (1988) in a study at Monroe County (Rochester, NY) found that for most of the affected subjects, Tourette's Syndrome was mild and required no drug treatment. These studies suggest that although Tourette's Syndrome may be a severe and disabling disorder, most cases are mild and do not come to medical attention (Kurlan, 1988).

Recent clinical and epidemiological studies of children with Tourette's Syndrome (Cohen et al, 1980; Jagger et al, 1982) have suggested that a sizeable percentage have attentional and learning difficulties. Comings and Comings (1987) noted that 62% of Tourette's Syndrome patients had Attention Deficit Disorder, and 48% had Attention Deficit Hyperactivity Disorder. In the majority of Tourette's Syndrome patients, the natural history of the disease was to start with Attention Deficit Hyperactivity Disorder and 2-4 years later develop motor and vocal tics. It is estimated that 10%-30% of Attention Deficit Hyperactivity Disorder is due to, or associated with, the presence of the Tourette's Syndrome gene (Comings and Comings, 1987). This hypothesis has, however, been questioned by various researchers (Pauls et al, 1987). Evidence that Tourette's Syndrome has a biological basis has stimulated

interest in a biochemical and genetic basis for the disorder. This recent evidence is based on the increased prevalence of learning disabilities, organic findings on psychological testing, neurologic "soft signs" and deviant EEG patterns (Shapiro, Shapiro, Brunn et al; Sweet, Solomon, Wayne et al, 1973: Wayne, Shapiro and Shapiro, 1972).

Tourette's Syndrome is considered a rare, hereditary, neurobehavioural disorder with heterogeneous clinical manifestations. Motor and phonic tics may assume a variety of forms and severity. Sensory phenomena are commonly associated with the motor manifestations. Chronic Multiple Motor Tics or Phonic Tic Disorder and Transient Tic Disorder most likely represent milder variants of the same illness (Robertson, 1989). Tics may be accompanied by a variety of associated behavioural disorders, such as Obsessive Compulsive Disorder, Attention Deficit Hyperactivity Disorder and Learning Disability. For some individuals, these behavioural disturbances may represent the predominant or only clinical manifestations of illness. Other behavioural disorders may also be part of the clinical spectrum of Tourette's Syndrome, but more likely represent secondary effects of the illness (Kurlan, 1988). The precise etiology is unknown, although neurotransmitter abnormalities, particularly dopamine, have gained recognition, the involvement of the limbic forebrain structures are appealing as the possible anatomical sites for Tourette's Syndrome.

Various pathophysiological mechanisms have been postulated as the underlying cause of Tourette's Syndrome. The proposed mechanisms have implicated biochemical, psychological, genetic, and neurochemical or neurological hypotheses. Studies of biochemical abnormalities in Tourette's Syndrome have implicated changes in central nervous system dopamine (Silder, 1980; Snyder, Taylor, Coyle et al, 1970), or central nervous system noradrenergic mechanisms (Cohen, Shaywitz, Caparulo, Moldofsky, Tullis & Lamon, 1974; Yeragani, Blackman and Baker, 1983). Studies supporting a neurological basis for Tourette's Syndrome have reported a high incidence of abnormalities on clinical neurological examinations and various neurodiagnostic procedures (Bornstein, King & Carroll, 1983)

A high percentage of children referred for treatment of Tourette's Syndrome also have problems with attention, activity and impulse control. Sleep problems were found in sufferers of Tourette's Syndrome, particularly those diagnosed as Attention Deficit Hyperactivity Disorder sufferers. Furthermore, a significant percentage of Tourette's Syndrome children had Attention Deficit Disorder. In the majority of Tourette's Syndrome patients, the natural history of the disease was to start with Attention Deficit Hyperactivity Disorder and later to develop motor and vocal tics (Comings & Comings, 1987).

It appears that Tourette's Syndrome is also a subtle neuropsychological deficit of unknown origin, like Sudden Infant death syndrome, which has overlap with Attention Deficit Hyperactivity Disorder and

Attention Deficit Disorder.

1.4   Attention Deficit Hyperactivity Disorder

Previously referred to as hyperkinetic syndrome, minimal brain damage, minor cerebral dysfunction, or hyperactive child syndrome,current views regarding these difficult to manage children emphasize attentional deficits in addition to the associated behaviour problems that characterize the disorder. Although controversy still surrounds the diagnosis and treatment of attention deficit disorders, it is generally agreed that there are a large number of children and adolescents who are fidgety,restless and have difficulty concentrating (Rostain,1991) Although it is the most widely studied behaviour disorder of childhood,its cause remains unclear,its outcome is variable, and its treatment is both complex and generally only modestly successful (Rostain, 1991).

Attention Deficit Hyperactivity Disorder currently represents one of the most frequently diagnosed neurobehavioural disorders in children, affecting perhaps as many as 20% of the school going population. Symptoms of Attention Deficit Hyperactivity Disorder, although subtle, are at the same time pervasive, influencing every aspect of the child's life - his home, school and relationships with peers (Rostain, 1991). Evidence from a number of investigative groups suggests a substantial overlap between Attention Deficit Hyperactivity Disorder and Attention Deficit Disorder and learning disabilities. The prevalence of learning disabilities in Attention Deficit Hyperactivity Disorder and Attention Deficit Disorder is estimated to be 9-10% in hyperactive boys (Halperin et al. 1984). Conversely, the prevalence of hyperactivity in learning disabled populations has varied from 41% (Holborrow & Berry, 1986) to 89% (Safer & Allen, 1976), with a prevalence of 33% reported in an epidemiological sample. Studies examining the academic achievement of hyperactive compared to control children support the idea that significantly more Attention Deficit Hyperactivity Disorder and Attention Deficit Disorder children experience academic achievement problems (Cantwell, 1978).

Attention Deficit Hyperactivity Disorder is a behaviourial concept with neurological implications: it must be labelled a "behaviourial" concept because it is defined by specific behaviourial characteristics, rather than by, as is generally the case in adult patients, by infra-behaviourial evidence of cerebral abnormalities (Benton,1987). The term Attention Deficit Hyperactivity Disorder is used as a medical designation for certain aberrations of behaviour and/or cognitive functioning resulting from milder forms of central nervous system dysfunction or developmental deviation (Clements & Peters, 1987). The term refers to children of near average, average or above average general intelligence with certain learning and/or behaviourial disabilities ranging from mild to severe, which are associated with deviations of function of the central nervous system. These deviations may manifest themselves by various

combinations of impairment in perception, conceptualization, language, memory and control of attention, impulse or motor function (Rostain, 1991). These aberrations may arise from genetic variations, biochemical irregularities, perinatal brain insults or other illnesses or injuries sustained during the period which is critical for the development and maturation of the central nervous system, or from unknown causes. These central nervous system alterations may be permanent, and manifest during the school years as a variety of learning disabilities (Clements & Peters, 1981).

There is an increased occurrence of minor or "soft" neurological signs in Attention Deficit Hyperactivity Disorder children, while the occurrence of classical (hard) signs is almost normal (Wender, 1971). The deviances include poor fine motor co-ordination, impaired visual motor co-ordination, poor balance, clumsiness, choreiform movements and poor speech (Prechtl and Swemmer, 1962). There is considerable evidence that Attention Deficit Hyperactivity Disorder has several distinct and separate etiologies (Rie & Rie, 1980). The syndrome may be produced by the following:

- Organic brain damage,
- Genetic transmission as a polygenetic abnormality,
- Fetal maldevelopment (Rie & Rie, 1980).

Furthermore, Attention Deficit Hyperactivity Disorder can accompany other childhood disorders. It also seems to result from the interaction of subthreshold amounts of the etiological components (Rie & Rie, 1980). As an infant the Attention Deficit Hyperactivity Disorder child's most conspicuous problem would be physiological functioning; he is apt to be hyperalert and irritable, he is apt to have "colic", crying frequently and being difficult to soothe; he is apt to have sleeping difficulties (which may be his most obvious abnormality) - he may have difficulty in falling or staying asleep, or he may awaken frequently and early. A developmental history of hyperactivity has been reported in more than half of Tourette's Syndrome cases (Shapiro and Shapiro, 1978). Thus, many Tourette's Syndrome sufferers would manifest certain symptoms common to Attention Deficit Hyperactivity Disorder cases.

Recently, considerable research has been done in an effort to establish organic factors as causative agents in the Attention Deficit Hyperactivity Disorder syndrome (McMahon, 1981). It was assumed that the excessive activity, emotional lability and deficient socialization in these children was associated with varying degrees of central nervous system damage. This conclusion resulted from the observation that children recovering from encephalitis often become hyperactive, irritable, destructive, and antisocial (Omen, 1973; Stewart, 1970). Mentally retarded children who suffered brain injury at birth or shortly after were more hyperactive, emotionally labile and perceptually impaired than the presumed "hereditary" retarded child. These "behavioural problems" were viewed as neurological soft signs - the

severity of which was assumed to be associated with cortical and subcortical lesions of varying degrees of severity (Omen, 1973; Werner & Strauss, 1941).

A child cannot have Attention Deficit Hyperactivity Disorder without manifesting behaviourial abnormalities. Kinsbourne (1986) states that findings indicate a relative delay in some aspect of neurological development as a result of slowed evolution of cerebral control of the relevant activity. Reitan and Boll (1986) maintain that selected behaviourial deficiencies of brain damaged children have been described in the literature for many years, but only recently have extensive comparisons of normal and brain damaged children been performed. The antecedents of neurodevelopmental dysfunction are many, and the particular patterns of affected functions does not indicate any particular pathogenesis. Nor are the antecedents of Attention Deficit Hyperactivity known to differ from those of major congenital central nervous system disorders such as cerebral palsy or mental retardation.

It appears that any influence that is deleterious to neurons can, if it has impact on the developing brain, retard the pace of some aspect of brain development. If it impairs mechanisms that are already functioning at birth, then the resulting clinical picture is abnormal irrespective of the stage of extra-uterine life (Kinsbourne, 1986). Research thus indicates a neuropsychological involvement in Attention Deficit Hyperactivity Disorder.

1.5   Attention Deficit Disorder

Attention Deficit Disorder is a residual category for disturbances in which the predominant feature is the persistence of developmentally inappropriate and marked inattention that is not a symptom of another disorder, such as mental retardation or Attention Deficit Hyperactivity Disorder, or of a disorganized and chaotic environment (Shaywitz and Shaywitz, 1992). Publication of DSM-111-R in 1987 blurred the distinction between attention disorder with and without hyperactivity by focusing primarily on Attention Deficit Hyperactivity Disorder, and relegating Attention Deficit Disorder to a category now termed Undifferentiated Attention Disorder (Shaywitz and Shaywitz, 1992). The reasons for the decision to demote Attention Deficit Disorder was because it was believed that it might represent a type of inattention believed to accompany the non-verbal learning disabilities, and so might be a new subtype of the existing category of Specific Developmental Disorders (Rourke, 1989). Rutter (1982) views Attention Deficit Disorder as a lesser variant of gross traumatic brain damage, a continuum notion and a syndrome notion, in which Attention Deficit Disorder constitutes a genetically determined disorder rather than a response to any form of injury.

Good evidence supports the differentiation between subtypes of Attention Deficit Disorder,

demonstrating that while Attention Deficit Hyperactivity Disorder and Attention Deficit Disorder children do not differ on independent measures of attention, Attention Deficit Hyperactivity Disorder and Attention Deficit Disorder demonstrate significantly different behaviourial, academic and social patterns (Edelbrock et al, 1984). Of particular interest, Lahey et al, (1987) indicate that Attention Deficit Disorder boys are rated by their teachers as manifesting a poorer school performance compared to Attention Deficit Hyperactivity boys, a finding supported by the high rate of retention.

Pasamanick and Knobloch (1966), using an earlier concept of Lilienfeld and Parkhurst (1951) described a "continuum of reproductive casualty" in infants, related to pregnancy and delivery complications, which at the less pathogenic end could produce mild forms of neurological insult undetectable by the usual diagnostic techniques, but which would contribute to a wide variety of subsequent maladaptions in children. Strauss and Kephardt (1955) observed that distractibility is often the most obvious difficulty in this regard. Hutt et al, (1963) were able to show not only that brain damaged children had a shorter attention span for playing with one object at a time but that they were less able to experience distractions without disruption of their task. The outward signs of distractibility and inattentiveness tend to disappear with age, but the problem tends to remain in more muted form (Wender, 1971). The characteristics manifested in infants later to be diagnosed as having Attention Deficit Hyperactivity Disorder are similar to those manifested in Tourette's Syndrome sufferers, Sudden Infant Death Syndrome victims and siblings. These findings are consistent with the notion of subtle central nervous system dysfunction in Sudden Infant Death Syndrome risk infants from the time of birth (Thoman et al, 1988).

It appears therefore that Sudden Infant Death Syndrome infants share many symptoms with their siblings, and that the possibility exists that a less lethal variant of this condition's central mechanism exists in the siblings of Sudden Infant Death Syndrome infants. These symptoms, on the other hand, often manifest as "soft" neurological or neuropsychological anomalies, showing a large degree of correspondence with those symptoms often found in Attention Deficit Hyperactivity Disorder, Attention Deficit Disorder and Tourette's Syndrome.

It is generally accepted that most psychological phenomena are multidetermined and are generally the products of the interaction of several factors. If an adequate amount of each of the putative causes can produce the Attention Deficit Hyperactivity Disorder syndrome, one might expect that the combination of subthreshold amounts of each factor might possibly do the same. Logic suggests that the interaction of forces is important. It is thus tenable that such an interaction occurring between non-genetic biological factors and a genetic predisposition to Attention Deficit Hyperactivity, Attention Deficit Disorder, Tourette's Syndrome and Sudden Infant Death Syndrome, might favour the development of

the phenomena.

Hyperactivity is defined as an excessive amount of gross motor activity and/or an excessive amount of inappropriate activity (Werry and Sprague, 1970). Hyperactivity may occur as a symptom in neurotic, schizophrenic or prepsychotic disorders, or it may occur in the behaviour disorders known as Attention Deficit Hyperactivity Disorder Syndrome and Tourette's Syndrome. Generally, children suffering from this syndrome exhibit normal intelligence, accompanied by short attention span, low frustration tolerance, and impulsive behaviour. They often perform poorly in school, are aggressive and have poor relationships with peers. Many of the same behaviour traits are manifested by Tourette's Syndrome sufferers (Kurlan, 1988).

1.6   Conclusion

Various studies which have reported abnormalities on various neurodiagnostic procedures provide support for the neurological etiological theories in Sudden Infant Death Syndrome, Tourette's Syndrome, Attention Deficit Disorder and Attention Deficit Hyperactivity Disorder. However, these studies fail to reveal any consistent pattern or specific abnormality to account for the disorders. Attention Deficit Hyperactivity Disorder as a neurodevelopmental disorder (Stander, 1989) shows many parallels with Sudden Infant Death Syndrome and Tourette's Syndrome. As in the case of Sudden Infant Death Syndrome and Tourette's Syndrome, Attention Deficit Hyperactivity Disorder and Attention Deficit Disorder also seem to show a confusing variety of neurophysiological and neurochemical factors in their etiology, also without a central theory or paradigm to account for the observed variances in the plethora of associated research findings. It appears from the above that Attention Deficit Hyperactivity Disorder, Attention Deficit Disorder, and Tourette's Syndrome children and a subgroup of siblings of Sudden Infant Death Syndrome infants manifest similarities in neurobehavioural, neural and behaviourial characteristics.

These conditions are all neuropsychological disorders of childhood which are relatively common among children. It appears that it could be seen as a disorder of neuropsychological disturbance with varying degrees of abnormality in the broad spectrum of abnormalities, resulting more specifically in various diseases and it is therefore important to conduct a study to determine what the degree of correspondence versus the degree of differentiation for these conditions is.

The aimt would therefore be important to ascertain whether there is a possibility that, given the broad similarities in subclinical brain damage resulting in neuropsychological anomalies, Sudden Infant Death Syndrome infants, Sudden Infant Death Syndrome siblings, Attention Deficit Hyperactivity Disorder

14

cases, Attention Deficit Disorder sufferers, and Tourette's Syndrome children might manifest similar neuropsychological problems. The correlation between potentially relevant factors (eg. sex, status, familial preference, pre- and perinatal complications, response to medication, neurological "soft signs", developmental precursors, and immaturity) is significant. It now appears possible that Sudden Infant Death Syndrome and Attention Deficit Disorder, Attention Deficit Hyperactivity Disorder and Tourette's Syndrome might be sub-categories of a common disorder, a "genetically neuropsychological risk condition". To further examine this possibility, it would be necessary to examine more closely the neurological and behaviourial correlates and consequences of non-overt brain damage, or "subclinical" brain damage. This will be covered in the following Chapter.

SYNDROMES IN PAEDIATRIC NEUROPSYCHOPATHOLOGY

2.1   Sudden Infant Death Syndrome

2.1.1   Definition

The Sudden Infant Death Syndrome refers to the unexplained death of a child in the first year of life, usually 1 to 6 months of age. The term "unexplained" means that there is no clear indication upon autopsy and upon review of the infant's developmental/paediatric history what was the cause of death. The infant simply stops breathing, usually at night, without apparent cause, and without any appreciable audible agonal response (Burns & Lipsitt, 1991).

Sudden Infant Death Syndrome is the most prevalent cause of death in infants between one and twelve months old. Most deaths attributed to Sudden Infant Death Syndrome occur between one and four months of age. Sudden Infant Death Syndrome is the leading cause of postnatal mortality in First World countries. Epidemiological, pathologic and physiologic data suggest the mechanisms of Sudden Infant Death Syndrome are complex, characterised by interaction at many levels of the neuraxis, between the organism and the environment, and spanning both pre- and post-natal life (Hoppenbrouwers & Hodgman, 1982). Factors unique to Sudden Infant Death Syndrome are: Age of death, association with sleep and increased risk for the second born Schwartz, 1987). A proposed core deficit consists of mild hypoxia, sustained during pre- and post-natal life, for which the majority of infants successfully compensate (Naeye, 1973).

However, previously not fully appreciated changes between one and three months of age in development and integration of the nervous system give rise to increased vulnerability to endogenous and exogenous deleterious influences at this time (Hoppenbrouwers & Hodgman, 1982).

2.1.2   Epidemiology

McMahon and Pugh (1970) define epidemiology as "the study of the distribution and determinants of disease frequency in man." Susser's definition is broader, "the study of the distributions and determinants of states of health in human populations". Both definitions focus on populations, because one should be able to enumerate all instances of the condition under study, within the population.

The epidemiological approach attempts to determine the frequency of a condition by relating the number of cases to an appropriate total population, and also to research how frequency varies according to such variables as age, sex, social class, ethnicity and geography. Secondly, epidemiologic study is analytic. Knowing the distributions of rates according to the kinds of variables mentioned above, hypothesis causes may be studied in order to test whether particular variables are causally associated with a given condition. This chapter is concerned with the epidemiology of Sudden Infant Death Syndrome. We shall assume that Sudden Infant Death Syndrome indicates such a disordered state of health (Kelly & Shannon, 1982).

By describing epidemiological factors that occur more frequently in the Sudden Infant Death Syndrome victims, it is possible that a classical high-risk state may be identified to prospectively determine infants more vulnerable to Sudden Infant Death Syndrome. There are several factors in Sudden Infant Death Syndrome victims that indicate that altered physiology is affected by the environment. Sudden Infant Death Syndrome occurs more frequently in infants whose parents are poor and under 20 years old, whose mothers are unmarried, have poor pre-natal care, are ill during the pregnancy, have short interpregnancy intervals, have previous fetal loss and who are smokers or abusers of narcotics (Kelly & Shannon, 1982).

The rate of death due to Sudden Infant Death Syndrome varies with ethnic background. In South Africa the general risk is 2 per 1000 live births. However, for poor blacks this figure is considerably higher, 8 per 1000 live births, while Orientals have a very low risk, 0,5 per 1000 live births (personal communication, Dr. Padayachee, Johannesburg City Health Department, 1989). These differences were attributed to socioeconomic factors (Valdes-Dapena, 1988). However, a study in Cook County, Illinois, North America, based upon an analysis of 1223 Sudden Infant Death Syndrome deaths, showed the rate to be 5:1 amongst blacks, 3:1 among whites, and only 2:1 among Hispanics, even though the Hispanics in this area are socially disadvantaged. The higher rate among blacks therefore cannot be attributed to education and income alone. It appears that cultural factors may also play some role (Valdes-Dapena, 1988).

A diversity of factors pertaining to the infant have been identified more frequently in Sudden Infant Death Syndrome victims. These include preterm birth, intra-uterine growth retardation, low Apgar scores, the need for oxygen and resuscitation at birth, being second or third in birth order or being the product of a multiple birth, specifically the second of a twin pair. Birth weight and zygosity are not contributing factors. Triplets are at greater risk. Several twin pairs have died on the same day. (Naeye, 1980). Smialek (1986) described 9 instances in which twin infants died of Sudden Infant Death Syndrome simultaneously. He maintains that this occurrence is a natural phenomenon, and not the result

of a criminal act.

Polberger and Svenningson (1985) raised as issue that has become increasingly obvious, the issue of Sudden Infant Death Syndrome among infants less than 28 days of age. The definition of Sudden Infant Death Syndrome makes no mention of age of the infant. From experience, it is known that the peak incidence is between 2-4 months and relatively few cases occur under 1 month of age. However, it does occur among infants born prematurely, who are being maintained in the institution until they are sufficiently mature to be cared for at home. Valdes-Dapena (1988) suggest that it is now advisable to include all inexplicable infant deaths in the rubric of Sudden Infant Death Syndrome to embrace in the concept of that phenomenon, all of the infant mortality involved. Polberger and Svenningson (1985) conclude that " these are probably cases of Sudden Infant Death Syndrome hitherto unrecognised in the first days of life." It is now considered that neonates present a small but significant segment of the total Sudden Infant Death Syndrome population.

The type of feeding, breast or bottle, has not been found to be a risk factor in Sudden Infant Death Syndrome. There is no difference in the incidence of age at death of breast or bottle fed infants (Biering-Sorensen, Jorgensen, Hilden, 1987). Epidemiologic investigators suggest that a number of perinatal and perimortal factors are more often seen in infant deaths from known and unknown causes. These observations suggest that these infants have experienced adverse influences prenatally which may make them peculiarly vulnerable to post-natal challenges.

2.1.3   Frontal Lobe Involvement

One of the leading hypotheses in Sudden Infant Death Syndrome research is that Sudden Infant Death Syndrome is due to a subtle defect in brainstem neural circuits which control respiration and/or cardiac stability during sleep (Kinney and Filiano, 1988). The unique age distribution of Sudden Infant Death Syndrome with a peak at 2-4 months, and the risk factors of prematurity and low birth weight suggest that maturational factors are involved (Hunt & Brouillette, 1987). Studies in normal infants show dramatic physiological changes in the neural control of respiratory patterns, cardiac rhythm, and sleep/waking states in the first six months of life. The timing of Sudden Infant Death Syndrome with these physiological changes suggest that there is a critical period in central nervous system development during which the infant is vulnerable to neurogenic sudden death. Attention is focused on the brainstem because it integrates respiration, cardiovascular stability, sleep and arousal, so closely that neurons regulating one function strongly influence others (Kinney & Filiano, 1988).

A proposed core deficit consists of mild hypoxia. This usually elicits successful compensatory behaviour

18

but over a period of time may render the infant more vulnerable to other risk conditions. The core deficit is mild and established as a result of influences during pre- and post-natal life. These influences include conditions in utero, mild perinatal insults, premature delivery and postnatal environmental conditions (Hoppenbrouwers & Hodgman, 1982). Successful compensatory behaviour by an infant may be challenged by a number of aggravating conditions, each of which alone, or in combination, can trigger decompensation resulting in death (Hunt & Brouillette, 1987).When the infant enters the time of integration of functional systems, it marks the end of the grace period of maternal immunological protection and is characterised by changing regulation of sleep organization and functional interacting with the environment. These profound alterations create instability and an organism which transiently can be more easily affected by internal or external influences. Hoppenbrouwers & Hodgman (1982) postulate a structural and functional "overshoot" in the development of forebrain areas as a compensatory response to an oxygen deficit. Whether due to dysmaturity or injury, it would be surprising if functional abnormalities were confined to respiration because brainstem areas that control respiration are not completely segregated from other vital centres, including arousal (Naeye, Ladis, Drage, 1976).

2.1.4 Perinatal Risks

There are several factors in Sudden Infant Death Syndrome victims that indicate that altered physiology is affected by the environment. The mothers of Sudden Infant Death Syndrome victims smoke excessively (Bergman & Weisner, 1976), have more difficulties during pregnancy (eg anaemia, infection, proteinuria), and have fewer pre- and postnatal appointments (Carpenter & emery, 1974; Lewak, Van den Bergh & Beckwith, 1979; Lipsitt, 1978; Naeye, Ladus et al, 1976) and have short interpregnancy intervals, (Carpenter, Gardner, McWenny & Emery, 1977; Spreis & Wang,1976). Information from personal interviews indicates an increase in alcohol abuse among fathers and grandfathers of Sudden Infant Death Syndrome victims (Chapman, 1991). There appeared to be a higher incidence of psychiatric disorders among the mothers of Sudden Infant Death Syndrome victims and evidence of Attention Deficit Hyperactivity and anti-social behaviour among the fathers (Chapman, 1991).

Other perinatal risks identified in Sudden Infant Death Syndrome victims include possible third trimester bleeding and maternal sedation or anaesthesia, feeding difficulties, hypotonicity and jitteriness (Kelly & Shannon, 1982). Much research identifies maleness as a risk factor (Arsenault, 1980; Biering-Sorensen, Jorgensen & Hilden, 1979; Froggatt, Lynas & Marshall, 1971). The ratio of male to female deaths among cot-death babies is 5:1 (Valdes-Dapena, 1985). The curve for age death among Sudden Infant Death Syndrome victims has long been considered unique. Goldberg et al (1986) compared this

19

curve with those for 21 other causes of infant mortality. They found the curve for Sudden Infant Death Syndrome babies to be significantly different from all others. They demonstrated that this curve was independent of other risk factors including race, gender, birth weight, seasonality, maternal age, month of gestation in which prenatal care was initiated and legitimacy of birth. The authors concluded that there is probably an important underlying mechanism related to growth and development in most cases which makes those particular infants highly susceptible between the ages of 2-4 months (Valdes-Dapena, 1988).

Sudden Infant Death Syndrome victims have been reported as being less responsive, have unusual cries as compared with siblings, and gain weight poorly (Naeye et al, 1976). The sounds were weaker, of shorter duration, and breathy. Extremely high pitched cries were often produced, abrupt changes in pitch, and the presence of more than one pitch was often noted. These features were seen as a suggestion of malfunction in the brainstem and part of the basic pathogenetic mechanism (Colton & Steinschneider, 1981).

2.1.5   Morphology

(1)   Dysplastic lesions

Vawter and Kozawich (1983) reviewed retrospectively gross and microscopic reports of infant autopsies in an attempt to identify dysplastic lesions including nevi, hemangiomas, nodular renal blastemas and neuroblastemas in situ. A significant proportion of the Sudden Infant Death Syndrome babies bore the lesions in question, while none of the infants who succumbed by trauma to aspiration had any of them (Hunt & Brouillette, 1987). The supposition is that Sudden Infant Death Syndrome infants have experienced some sort of minor adverse influence during intrauterine development, which resulted in the abnormality. These flaws or minor aberrations reflect a minimal prebirth insult that the intrauterine injury, which may vary from individual to individual, is one element in the cause of the infant's death. The concept that intrauterine injury is involved in the genesis of Sudden Infant Death Syndrome is gaining acceptance with researchers involved in the study of this phenomenon. It is speculated that Sudden Infant Death Syndrome babies begin to experience difficulty before birth and from the day of birth many of them manifest subtle abnormalities (Schwartz, 1987).

(2)   Dysmorphic lesions and minor irregularities

Moltz et al (1984) undertook a similar study to that undertaken by Vawter and Kozawich (1983). However, they included dysmorphic lesions such as hernias and hydroceles and minor anomalies like

bifid uvula and Meckel's diverticulum. They found the difference between Sudden Infant Death Syndrome infants and controls to be significant. This research augments the conviction that many Sudden Infant Death Syndrome victims are structurally flawed and have been affected in some detrimental manner before birth.

(3)   Cytomegalovirus infection

Four apparently healthy infants whose deaths seemed unexpected and unexplained, were described by Variend and Pearse (1986). However, all four were found to have microscopic aggregates of inclusion-bearing cells pathognomic of Cytomegalovirus infection in extraneural organs. There was no associated tissue destruction in those sites, so the authors concluded that those lesions had not led to the infants' demise. However, the brainstem in each showed small numbers of glial nodules which led to the authors theorizing that comparable lesions might have interfered with the vital function of some critically located neurons and thus had been responsible for the infants' death. They further speculated that those nodules might represent "scars" of preexisting inflammatory lesions, which might possibly have been acquired in utero (Valdes-Dapena).

Huff (1986) reported a retrospective study of 401 infant autopsies in which he found Cytomegalovirus cells microscopically in seven percent of the Sudden Infant Death Syndrome babies and only one percent in the explained deaths. Furthermore, on reappraising the autopsies on those infants with Cytomegalovirus infection, he found that 64% of the total comprised babies from the smaller group of Sudden Infant Death Syndrome victims. These two recent studies raise an important question. Is previously unrecognized intrauterine Cytomegalovirus infection (perhaps via scarring in the brainstem) responsible for some crib deaths? The hypothesis that it is , seems tenable (Valdes-Dapena, 1985).

(4)   Pulmonary congestion

This condition is characterised by engorgement of the pulmonary vessels with transudation of fluid into the alveolar interstitial spaces. It occurs in cardiac disease, infections and certain injuries (Dorland, 1989). This condition has always been considered one of the foremost morphologic characteristics of typical Sudden Infant Death Syndrome. However, review of the data showed that severe congestion was apparent in 99% of the 385 Sudden Infant Death Syndrome deaths, but in 100% of the 6 explained deaths. There is no significant difference between the two groups, therefore this feature is not a major contributing factor (Valdes-Dapena, 1988).

(5)   Pulmonary edema

This condition is characterised by diffuse extravascular accumulation of fluid in the pulmonary tissues and air spaces due to changes in hydrostatic forces in the capillaries or to increased capillary permeability. It is marked by intensely laboured or difficult breathing (Dorland, 1989). Pulmonary edema is also thought to figure prominently in the typical Sudden Infant Death Syndrome death autopsy. However, virtually no difference was found between Sudden Infant Death Syndrome victims and a control group (Naeye, 1980), leaving this possibility with no explanatory value.

(6)   Thymic petechiae

This condition is characterised by minute red spots on the chest due to the escape of a small amount of blood (Dorland, 1989). Petechiae were noted in 52% of Sudden Infant Death Syndrome deaths but in none of the explained deaths. This finding confirms the long held idea that these thoracic petechiae are distinctive, unique and an unusual feature of these infants that might be divulging something about the way in which they die. However, according to the data, almost half of the Sudden Infant Death Syndrome babies do not have thymic petechiae. The investigator can only conjecture on how that occurrence is to be explained (Valdes-Dapena, 1988).

(7)   Metabolism

Metabolic difficulties have been postulated as a possible cause of Sudden Infant Death Syndrome (Valdes-Dapena, 1988). Herein the death is postulated to occur as a consequence of deficit or defect in the chemical process that takes place in the body as relates to the movement of nutrients in the blood after digestion, resulting in deficits in growth, energy, release of wastes and other body functions. Studies on electrolytes, urea nitrogen, and protein in vitreous humour, concentrations of selenium, zinc, copper, calcium and magnesium in serum and liver and concentration of 25 hydroxyvitamin D, failed to reveal a significant difference between Sudden Infant Death Syndrome victims and control infants (Hillman, Erickson, Haddad, 1980). Hypoglycaemia was discarded as a cause of Sudden Infant Death Syndrome by Naeye (1980) when he found no difference in plasma cortical or growth hormone in Sudden Infant Death Syndrome victims. Investigation of thiamine metabolism in Sudden Infant Death Syndrome, prompted by the fact that subacute necrotizing encephalomyelopathy (Leigh's Disease) is identified with abnormal control of vitiation and defects in thiamine dependent brainstem metabolism are still inconclusive (Read, 1978).

Toxicology researchers have found no toxic levels of barbiturate, opiate, ethanol or organic basis in a significant number of Sudden Infant Death Syndrome autopsies (Smialek & Monforte, 1977). It has found, however, that more deaths occur among infants born to methadone addicted mothers (Cavex,

Ostrea, Stryker & Smialek, 1979). At autopsy, however, no trace of the drug is found, suggesting that methadone may continue to have an effect after clearance from the blood, or that maternal drug addiction is associated with another factor that increases infant mortality. On the other hand, Olsen and Lees (1980), found that methadone depresses brainstem regulation of breathing in infants, suggesting the possibility that pregnant mothers in cocaine withdrawal programmes could have children with difficulties in the regulation of breathing. Rajegowda et al (1978) suggest that intrauterine exposure to narcotics and its subsequent effect on central control of respiration in the young infant may be the underlying mechanism for drug-related cases of Sudden Infant Death Syndrome.

The incidence of Sudden Infant Death Syndrome is higher amongst smoking mothers than non-smoking mothers (Naeye, Ladus, Drage, 1976). The concentration of carboxyl-hemoglobin associated with abnormal placental and umbilical arteries in these babies is 80% higher than in the mothers. Smoking has also been associated with placental previa, and abruptio, preterm birth, and small for gestational age infants (Comstock, Shah, Meyer & Abbey, 1971). These factors could play a role if only a contributory one, to the causation of Sudden Infant Death Syndrome, or at least exacerbate an existing pathological condition.

Autopsies on Sudden Infant Death Syndrome infants evidence no toxic substance in tissue or plasma (Kelly & Shannon, 1982), but there is an increased Sudden Infant Death Syndrome death rate associated with methadone and cigarette use during pregnancy. This would serve to reinforce the opinion that certain lifestyle factors influence the development of Sudden Infant Death Syndrome.

2.1.6   Placental Pathology

Naeye (1977) mentions that placental pathology or deficiency might account for the development or lack of development of certain factors that would lead to Sudden Infant Death Syndrome. He suggested that the placentas of infants who succumbed to Sudden Infant Death Syndrome were abnormal in that they manifested an increased evidence of chomoamnionitis. In 1987, Denmead, Ariagno, Carson & Benirschke examined the placentas of 27 Sudden Infant Death Syndrome babies and compared the findings. They found no significant increase in chomoamnionitis or any other irregularity in the placentas of the Sudden Infant Death Syndrome victims. The authors note that it is important to control for prematurity because it is so strongly associated with chomoamnionitis. This probably accounts for the difference between the results obtained a decade ago and the more recent results, therefore suggesting that this cadre of hypotheses are somewhat lacking in sufficient support to be considered seriously as a cause of Sudden Infant Death Syndrome.

2.1.7　Fetal Hemoglobin

Guillian al (1987) reported that virtually all Sudden Infant Death Syndrome victims have higher than normal levels of fetal hemoglobin, which, if confirmed, may permit identification of the potential victim before the fact. He found elevated fetal hemoglobin levels in 59 infants who had died from Sudden Infant Death Syndrome. The 40 controls showed no elevation. Only 5 of the 59 victims had hemoglobin F levels within the range of normal and all were above the mean. None of the 40 controls had levels outside the normal range. Deviation from normal levels increased with age and was most apparent in those infants who died after 50 weeks post-conceptional age. It was concluded that fetal hemoglobin levels may serve as a prospective marker for some infants at risk for Sudden Infant Death Syndrome.

This study caused some interest among researchers as there is hardly any overlap between hemoglobin F levels among cases and those among controls. Five of the Sudden Infant Death Syndrome infants had levels within the normal range and those were above the mean. In no other manner are Sudden Infant Death Syndrome babies so homogeneous, or so different from living babies. If hemoglobin levels are abnormally elevated in more than 90% of Sudden Infant Death Syndrome victims, as indicated, the implications of the finding are incalculable. It would enable scientists to identify a great majority of the victims beforehand, thus permitting them to examine these infants and ascertain in what way their physiological functions are abnormal. A breakthrough in this area could lead to the total resolution of the problem. However, more research in this area is necessary and thus confirmation of the observation (Valdes-Dapena, 1988).

2.1.8　Current hypotheses related to Sudden Infant Death Syndrome

(1)　The Apnea Hypothesis

This is a respiratory theory that enjoys the widest general support as the main cause of Sudden Infant Death Syndrome. According to this, Sudden Infant Death Syndrome is caused by sudden, spontaneous apnea, favoured by sleep. Central and obstructive apnea have been implicated. Abnormalities in the control of central ventilatory muscles during sleep have been suggested, as well as defects in the arousal mechanism involving the reflex response to mild hypercapnia or hypoxia (Shannon & Kelly, 1982). The main support for the apnea hypothesis results from a series of pathologic findings and from infants suffering a "near-miss."

The system that supplies oxygen and removes carbon dioxide in reaction to metabolic demands, is composed of controllers and end-organs. Although classically the primary respiratory centre is thought

to be located within the medulla, additional regulatory influences from the pons and higher brain centres have been demonstrated (Mitchell & Berger, 1975). These work together with the pontomedullary pacemakers (Wyman, 1977). Deficient control by the central chemoreceptors can result in severe hypoventilation during sleep and absence of the carotid bodies can result in prolonged voluntary breath-holding, loss of ventilatory response to hypoxia and mild hypoventilation (Kelly & Shannon, 1982). Obstruction of vagal activity would result in hypoventilation and depressed ventilatory response to carbon-dioxide breathing and would eliminate the cough, Hering-Breuer inflation and laryngeal reflexes, which prevent the lungs from over or under inflation. Kelly and Shannon (1982) observed chronic underventilation and blunted respiratory responses to increased levels of inhaled carbon dioxide in infants who later died from Sudden Infant Death Syndrome. This evidence suggests that the infants had abnormalities in the control centres of the brainstem that normally respond to accumulations of carbon dioxide by increasing the frequency and depth of breathing (Kelly & Shannon, 1982).

There are changes in the respiratory system during sleep that are inclined to encourage apnea and hypoventilation. During active or rapid eye movement (REM) sleep, the skeletal muscle tone, including the pharyngeal constrictors and tongue, is suppressed, encouraging increased resistance and obstruction in the upper airway (Sullivan, Zamel, Kozar, 1979). Naeye (1980) states that reasons for the sudden death phenomena being more frequent in the first months of life have been found. In the first months, certain mechanisms of respiratory control operate differently from the way they do when the infant is older. In infants between 1-6 months old, the lungs partly collapse in the phase of sleep when the eyes move rapidly under the eyelids, because in this phase, the intercostal muscles that move the chest stops moving, so that respiration is interrupted during rapid-eye-movement sleep, little residual air remains in the lungs to continue the normal exchange of oxygen and carbon dioxide. The result is hypoxemia within a few seconds. An adult can stop breathing for from 30-40 seconds without developing severe hypoxemia. When breathing slows down or stops, the reflexes that augment it, or restart it in older children are noticeably less active in young children. Therefore, the survival of these babies depends on a reflex arousal out of rapid-eye-movement sleep and switching on of the brainstem mechanisms that restart breathing (Naeye, 1980).

With these factors as causes, different forms of apnea occur, possibly causing Sudden Infant Death Syndrome. There are prolonged apnea, obstructive apnea and mixed apnea. Prolonged apnea is defined as a respiratory pause with no chest or air movement for 15 seconds or longer, associated with cyanosis or pallor. Obstructive apnea is disruption of ventilation composed of lack of air flow, but continued respiratory movements. Mixed apnea is central apnea with a number of obstructed breaths, usually when breathing begins. The cause of these abnormalities is unknown, but several studies indicate that the

system governing ventilatory muscles, and perhaps upper airway muscle tone during sleep, is abnormal. Shannon et al (1977) reported a less than optimal increase in ventilation in response to hypercarbia and hypoxia, indicating that subtle abnormalities in neurologic control of breathing are implicated. Neurologic control of breathing is most often studied by measuring the increase in breathing associated with increasing carbon dioxide (hypercapnia) or decreasing oxygen (hypoxia). Other studies report a defect in arousal that relies on reflex response to mild hypercarbia and/or hypoxia and in control of the muscles of the upper airway, resulting in death. These findings suggest the hypothesis that the failure to arouse in response to a respiratory pause, or potentially dangerous hypoxic episode could prevent the infant from "rescuing" himself from the event (Guilleminault, Korobkin, Ariagno, 1979). Kelly and Shannon (1982) speculate that the explanation for the co-existence of these two abnormalities is a lesion in the brainstem, in the area of the medullary chemoreceptors and in the area that coordinates the innervation of the muscles of the upper airway and chest wall and their response to chemical stimuli, suggesting that hypoxia has affected the brainstem structures involved in the regulation of breathing. An abnormality in the tone of the upper airway muscles could also result in an increased resistance, thus encouraging hypoventilation and obstruction in infants with slightly decreased chemoreceptor activity, resulting in more tissue hypoxemia and pathologic changes in some body tissues from this chronic desaturation.

Anderson and Rosenblith (1971) suggest that the infant's inability to establish or maintain oral breathing with nasal occlusion, was a cause of Sudden Infant Death Syndrome. Herein, death occurs when the infant does not resort to oral breathing when nasal occlusion occurs. One may conjecture that abnormalities in chemoreceptor control and/or innervation of the muscles of the airway should result in hypoxemia, which should result in gasping and in arousal to a state in which sufficient breathing should be established. For these abnormalities to result in death, the responses to hypoxemia must also be deviant. Evidence has shown that this is the case in "near-miss" Sudden Infant Death Syndrome infants, (Hunt, McCulloch & Brouillette, 1982) preterm infants and in new-born lambs (Shannon,1980). A "near-miss" Sudden Infant Death Syndrome infant is an apparently healthy infant who experiences an episode of apnea during sleep, accompanied by a change in colour and tone, and who remains unresponsive to gentle stimulation, mouth to mouth resuscitation or prolonged vigorous shaking. The infant seems to have died, but his life is apparently saved by timely intervention, often by the parents.

Steinschneider (1972) first published his research findings with 5 infants who experienced episodes of central apnea in his sleep laboratory. Consequently, two of the infants died, unexpectedly and inexplicably. Their autopsies proved negative. He consequently proposed that central apnea was probably responsible foe many, if not most, Sudden Infant Death Syndrome deaths. His idea was

26

promptly named the apnea hypothesis.

Paediatricians accepted the hypothesis eagerly because it appeared that the problem of Sudden Infant Death Syndrome might be eliminated, or alleviated by the use of home monitors for infants judged to be at risk because of apneic episodes (Kelly & Shannon, 1982). Weitzman of Monefiore Hospital and Medical Centre observed that the apnea of sleep described by Steinschneider, resembled a condition experienced by adults who have chronic abnormalities in the control of respiration. Such adults typically underventilate their lungs during sleep. It was hypothesized that Sudden Infant Death Syndrome might do the same (Naeye, 1980). Naeye (1980) postulated that underventilation of this kind would leave anatomical markers. His research showed that 60% of the victims had an abnormal increase in muscle of the small pulmonary arteries. He maintained that this increase is caused by a chronic underventilation of the lungs. This underventilation reduces the level of oxygen in the air spaces of the lungs, causing nearby arteries to constrict. When a chronic underventilation prolongs the constriction, the number of muscle cells in the walls of the arteries increases (hyperplasia) Hyperplasia increases the resistance of the vascular system to the flow of blood through the lungs, which causes the blood to rise in the right ventricle of the heart (Naeye, 1980). The heart reacts like the pulmonary arteries by increasing the amount of muscle in the right ventricular wall. The abnormalities of both the pulmonary arteries and the heart were not considered important in early cases of Sudden Infant Death Syndrome (Naeye, 1980).

Underventilation that reduces the level of oxygen in the pulmonary air spaces results in a lowered level of oxygen in the arterial blood that circulates throughout the body. The idea that many babies who succumb to Sudden Infant Death Syndrome have experienced repetitive apneic episodes prompted Naeye (1980) to investigate for morphologic indicators of oxygen deficiency in such infants at autopsy. Shortly he was able to demonstrate what he considered to be substantial support for the apnea hypothesis in the form of seven apparent "tissue markers", or indicators of chronic oxygen deficiency in those necropsies.

They are the following:

- hypertrophy and hyperplasia of the muscular media of small pulmonary arteries;
- right ventricular hypertrophy;
- pathologically prolonged retention of periadrenal brown fat;
- hepatic erythropoiesis;
- hyper or hypoplasia of glomic tissue in the carotid body;
- hyperplasia of chromaffin tissue in the adrenal cortex; and
- brainstem gliosis (Naeye, 1980).

The above are pathological terms for conditions indicative of chronic oxygen deficiency. The first refers to the enlargement or the abnormal increase in the number of normal cells, in normal arrangement of the muscular media of the small pulmonary arteries. This results in a greater than normal muscle in the small pulmonary arteries. Right ventricular hypertrophy is the enlargement of the right ventricle, perhaps as a result of lung disease, as the right ventricle has difficulty pumping blood to the lungs. The third indicator refers to the retention of brown fat around the adrenal gland.

Brown fat surrounds certain vital internal organs at birth and is specially adapted for the generation of heat. Brown fat is given its characteristic colour under the microscope by the many intracellular particles known as mitochondria contained in the fat cells. Generally, the mitochondria is lost during the first year of life, after which the cells lose their distinctive brown colour. Infants who are chronically hypoxemic after birth exhibit fat cells that retain their mitochondria and brown colour (Naeye, 1980). These brown fat cells are normally replaced by white fat cells after birth (Naeye, 1976). This abnormality is probably secondary to chronic hypoxemia (Naeye, 1976). Hepatic erythropoiesis is the production of red-blood cells by the liver and increase in the production of red cells of the bone marrow. The liver does not normally manufacture red cells after the first week of life. This is a further sign of chronic hypoxemia in Sudden Infant Death Syndrome infants. These effects presumably occur because hypoxemia causes the kidneys to release erythropoeitin which stimulates the manufacture of red cells (Naeye, 1980).

Another indicator of chronic hypoxemia is an enlarged mass of glomic tissue in the carotid artery. The carotid, a small organ in the neck, has an important role in respiration. Many Sudden Infant Death Syndrome infants were found to have underdeveloped carotid bodies. If this organ does not function adequately, the infant may not be able to restart its breathing during a prolonged period of apnea. Possibly the lack of stimulation of nerve impulses coming to the carotid body from the respiratory control centres in the brainstem are responsible. Any abnormalities in the respiratory control centres are probably subtle, as an infant with severe abnormalities in this area would not survive after birth because they are closely associated with other centres that control other vital functions (Naeye, 1980). An enlarged mass of chromaffin cells in the adrenal medullas which manufactures adrenalin was also observed. An increase in the release of adrenalin (epinephrine) from the adrenal gland could possibly explain the retention of brown fat in babies who die of the syndrome, as brown fat usually reappears in adults who have a high level of epinephrine in the blood as a result of an adrenal tumour (Naeye, 1980). Furthermore, he found an abnormal proliferation of astroglial fibres in the lateral reticular formation of the brainstem. This region is an important centre for respiratory control. Naeye (1980) suspected that the astroglial proliferation was evidence of damage to respiratory control mechanisms.

28

However, he felt that such an interpretation could be inappropriate, as many other areas of the brainstem also exhibit the condition in infants who die from the syndrome. Furthermore, this condition is produced by chronic hypoxemia. Takashima et al (1977) found the greatest proliferation of astroglial fibres in Sudden Infant Death Syndrome infants in the areas where the blood supply is poorest.

Naeye (1980) postulated that the primary abnormalities responsible for Sudden Infant Death Syndrome are in the brainstem or the carotid body. The primary injury or defects could be genetic or result from damage sustained during pregnancy, labour, or delivery. The brainstem is a particularly vulnerable target for damage during fetal life, because it has a higher metabolic rate than other areas of the brain. This area is vulnerable to damage by low levels of both oxygen and glucose in the blood (Fuller, Guthrie, & Alvord, 1983). These lesions are more likely to be secondary to chronic hypoxemia than to be its cause. Increased astroglial proliferation is one of the well-known consequences of chronic hypoxemia (Brand & Bignami, 1969).

Researchers have attempted to duplicate Naeye's work subsequently. The result is that two of the "markers" have been shown not to be present in many Sudden Infant Death Syndrome deaths, namely: hypertrophy and hyperplasia of the muscular media of small pulmonary arteries; and right ventricular hypertrophy (Singer, Tilly, 1984). However, three have been confirmed, specifically pathologically prolonged retention of periadrenal brown fat, hepatic erythropoiesis, and brainstem gliosis (Kinney,Burger, Harrell, & Hudson, 1983). Studies in "near-miss" infants found a variety of abnormalities in respiratory functions. All types of apnea, hypoventilation, insufficient increase in ventilation during exposure to hypercapnia or hypoxia, and other abnormal breathing patterns have been described in this group (Shannon & Kelly, 1982). These results, collectively, have strengthened the concept of the apnea hypothesis.

Most interesting however, is the issue of brainstem gliosis. Valdes-Dapena (1988) considers it important to pursue this issue further because of the crucial role of various brainstem centres in the control of vital physiologic functions, particularly the control of breathing, arousal from sleep, heart beat and swallowing. This broadly-based hypothesis which would account for Sudden Infant Death Syndrome suggests that this phenomenon may be the result of abnormal brainstem neuroregulation of cardiorespiratory control. Data that does not support the apnea hypothesis has also been reported. Southall et al (1983) found that none of the infants who became Sudden Infant Death Syndrome victims showed prolonged apnea.

Undetected prolonged apneic episodes have also been detected in a small proportion of preterm infants

29

at the time of discharge from hospital (Southall et al, 1982). Though none of the infants who died from Sudden Infant Death Syndrome in the study by Southall et al (1983) showed prolonged central apnea (cessation of breathing for periods longer than 20 seconds) further studies on respiratory patterns rather than just the longest apneic episode are necessary, before any conclusion can be reached regarding respiratory control and prediction of Sudden Infant Death Syndrome. Prolonged apnea detected after a "near-miss" episode may be the result of the episode rather than the cause. A more detailed study of heart rate and breathing patterns of infants who suffer from Sudden Infant Death Syndrome is required.

Therefore it appears from the research that studies of Sudden Infant Death Syndrome victims and "near-miss" infants who subsequently died manifest tissue changes consistent with chronic hypoxia and hypoxemia. Physiologic studies of certain near Sudden Infant Death Syndrome infants demonstrated abnormalities in the control of ventilation and in the functioning of the muscles of the upper airway. Multiple episodes of central, mixed and obstructive apnea leading to desaturation of hemoglobin are the result of these abnormalities (Kelly & Shannon, 1982). This would cause a lack of oxygen to the brain. Hypoxia can result in acute pulmonary vasoconstriction and eventually hypertrophy in the pulmonary vasculature, resulting in an increase in ventricular afterload, and eventually to a decrease in cardiac output which can cause further hypoxia (Southall, 1983).

Another result of hypoxia is astrocyte proliferation in the brainstem, in the areas controlling ventilation, promoting hypoventilation and resulting in further hypoxemia, causing further damage. Consequently, decreased cardiac output during hypoxemia and abnormal function of the medullary chemoreceptors can eventually be fatal, by severely affecting the amount of oxygen reaching the brain. The cause of these abnormalities appear to be unknown. However, as Sudden Infant Death Syndrome is statistically associated with maternal smoking, and placental abnormalities, as well as the need for oxygen at birth, this might be an indication that prenatal or perinatal asphyxia-hypoxemia may be the initial insult to the brainstem (Naeye, 1976).

A causal relationship between prolonged apnea and Sudden Infant Death Syndrome has not been established. However, there is no doubt that the apnea theory provides a valid mechanism for certain cases of Sudden Infant Death Syndrome and that a breathing abnormality may contribute to Sudden Infant Death Syndrome. The percentage of Sudden Infant Death Syndrome cases that can be ascribed to a primary respiratory cause remains to be evaluated. Dr. H. Kinney of Boston Children's Hospital has undertaken a five year research study involving the reconstruction of the brainstems of Sudden Infant Death Syndrome victims and controls, in an attempt to resolve this point (Valdes-Dapena, 1988). If her work reveals that there are structural abnormalities in the brainstems of certain of these infants,

another question is raised; Is the gliosis the cause of some fundamental physiologic malfunction, and therefore the cause of the infant's demise, or the result of some fundamental physiologic malfunction, or both? However, it appears to be vitally important that the presence or absence of brainstem gliosis in these infants be established.

In conclusion, this central hypothesis of Sudden Infant Death Syndrome has yielded several quantitative abnormalities in neuropathological studies of Sudden Infant Death Syndrome victims that make brainstem analysis more compelling than ever. Brainstem gliosis, and dendritic spine neurotransmitters and vagal nerve alterations are important clues that must be thoroughly explored.

(2)   The Cardiac Hypothesis

Fraser and Froggat (1966) suggested that genetically determined abnormalities of cardiac conduction might be involved in Sudden Infant Death Syndrome. In this case Sudden Infant Death Syndrome would be caused by fatal arrhythmias or conduction disorders, primarily the result of developmental changes in critical areas of the conduction system (James, 1968). However, in 1973, Froggat and James seriously questioned these findings. They examined the likelihood that Sudden Infant Death Syndrome infants die as a result of a lethal arrythmia produced by failure or disturbance in the usual electrical activity of the heart. They concluded that the cardiac hypothesis is no less likely than others in which Sudden Infant Death Syndrome is attributed to respiratory causes.

Schwartz (1976) suggested that developmental abnormalities in the cardiac sympathetic innervation may encourage the genesis of fatal arrhythmias, in some cases of Sudden Infant Death Syndrome. An hypothesis relating some developmental aspects of cardiac innervation to sudden death during infancy was suggested by Schwartz (1976). Later, one of the aspects was taken to characterise the entire hypothesis, which became known as the QT hypothesis. The genesis of this hypothesis is in the proposed pathogenetic mechanisms of the idiopathic long QT syndrome - the most interesting example of neurally mediated non-coronary sudden death occurring in apparently healthy individuals with a negative post-mortem examination (Blumenfield, Mantell et al, 1978). An hypothesis relating some developmental aspects of cardiac innervation to sudden death during infancy was presented in 1976 by the American Academy of Paediatrics Task Force on prolonged apnea. There appears to be an apparently close relationship between the autonomic nervous system and sudden death (Schwartz, 1982). It was suggested that some Sudden Infant Death Syndrome fatalities might result from ventricular fibrillation caused by a sudden increase in sympathetic activity affecting a heart with reduced electrical stability. The specific mechanism proposed was an imbalance between right and left cardiac sympathetic

nerves, resulting in a left-sided dominance. This type of imbalance is quite arrythymogenic, facilitates ventricular fibrillation, and often manifests itself in prolongation of the QT interval, which is associated with a particularly high risk of sudden death under a variety of circumstances (Schwartz, 1981).

The possibility of a time-limited imbalance in the cardiac sympathetic innervation suggests that these infants would be at high risk for Sudden Infant Death Syndrome, but only for a specified period of time. If they survive the high-risk period, they may have a completely normal life. The sympathetic imbalance hypothesis represents one specific aspect of a wider concept, that of developmental abnormalities in cardiac innervation that would curb the electrical stability of the heart and predispose some infants to ventricular fibrillation (Schwartz & Stone, 1985). The indicators of this sympathetic/ parasympathetic imbalance would be a higher than normal heart rate, reduced beat to beat variability, or an impaired baroflex sensitivity.

Some researchers have reported prolonged QT syndrome in certain Sudden Infant Death Syndrome victims (Southall et al. 1979). Other researchers have not confirmed this finding (Steinschneider, 1978), nor has prolongation of the QT intervals in siblings of Sudden Infant Death Syndrome victims or near Sudden Infant Death Syndrome infants been found (Kelly et al, 1977). This imbalance may represent instances of the idiopathic QT syndrome to be symmetrical and homogenous in most infants, however, this distribution probably follows the Gaussian or normal curve, as do most biological phenomena. Infants with the lowest right cardiac sympathetic activity would be the infant at the greatest risk for life-threatening arrhythmias and sudden death. They are likely to show a constant or paroxysmal prolongation of the QT interval. The right and left sympathetic neural pathways may occasionally develop at different rates. In this event, a delay in the right side or a temporary imbalance of the potentially lethal type described above.

There has also been some research of heart rate and heart rate variability in normal infants, Sudden Infant Death Syndrome siblings and near Sudden Infant Death Syndrome infants. An increased heart rate during sleep has been reported in Sudden Infant Death Syndrome siblings and in near Sudden Infant Death Syndrome infants compared with controls of only a few beats a minute (Leistner et al, 1980). A decreased heart rate variability during both active and quiet sleep up to 4 months of age has been reported in the near Sudden Infant Death Syndrome infants. These small differences are not lethal but could indicate altered autonomic regulation of heart rate, thereby causing stimulation of the nervous vagus. However, Hoppenbrouwers et al, (1979) found no variances in heart rate, suggesting that either the method of analysis was not sensitive enough to measure the differences, that the abnormal pattern may develop after birth, or that heart rate changes in the near Sudden Infant Death Syndrome infant

specifies a subset of Sudden Infant Death Syndrome.

The respiratory and cardiac mechanisms possibly involved in Sudden Infant Death Syndrome are not mutually exclusive and seem to be the largest contributors to the whole of Sudden Infant Death Syndrome, even if their specific importance still remains to be measured. As these two hypotheses appear to be the most likely possibilities, it would be logical to concentrate the research efforts on this field. The concepts of data presented above suggest that the sympathetic imbalance hypothesis, although not established, has gained support on the basis of current knowledge. The potential for early identification of potential Sudden Infant Death Syndrome victims and the possibility, if the hypothesis is correct, of developing an efficient and safe preventive strategy, makes a precise and unbiased evaluation of the cardiac hypothesis imperative.

(3)   The Brainstem Hypothesis

The brainstem hypothesis of Sudden Infant Death Syndrome is essentially an extension of the apnea theory. This hypothesis indicates that Sudden Infant Death Syndrome is the result of a subtle defect in the brainstem neural circuits which control respiration and/or cardiovascular stability during sleep. The unique age distribution of Sudden Infant Death Syndrome with a peak at 2-4 months, and the hazards of prematurity, and low birth weight suggest that maturational factors are involved, in as much that dramatic physiological changes in the neural control of respiratory patterns, cardiac rhythm and sleep/waking states in the first 6 months of life have been found in studies of normal infants. This indicates that the occurrence of Sudden Infant Death Syndrome with these physiological changes indicates a critical period in central nervous system development during which the vulnerability to neurogenic sudden death in the infant is apparent. The brainstem is focused upon, because it contains the principle sites which regulate cardiorespiratory activity during sleep. The brainstem integrates respiration, cardiovascular stability, sleep and arousal, so closely that neurons regulating one function strongly influences others, therefore, a deficit in any of these neurons may produce complex effects upon many functions (Kinney & Filiano, 1988).

Krous and Jordan (1984) suggest that the brainstem hypothesis accounts for the existence of intrathoracic petechiae and pulmonary edema in the majority of Sudden Infant Death Syndrome victims. The presence of intrathoracic petechiae indicates that an element of obstructive apnea occurs, as breathing against a closed airway can produce changes in intrathoracic pressure and microvascular rupture (Beckwith, 1973). Brainstem pathways aid control of upper airway patency during sleep and thus obstructive apnea does not exclude a brainstem involvement in Sudden Infant Death Syndrome.

33

Intrathoracic petechiae in Sudden Infant Death Syndrome may also be the result of hypoxia - induced endogenous catecholamine release (Krous et al, 1984). Neurogenic mechanisms which involve brainstem sites can similarly be implicated in the pathogenesis of pulmonary edema. The brainstem hypothesis does not assume that the Sudden Infant Death Syndrome victim has suffered apnea prior to the final lethal event. Nevertheless, infants with sleep-related respiratory dysfunction or cardiac rhythm disturbances who die suddenly, comprise a subset of Sudden Infant Death Syndrome that is important to deciphering cardiorespiratory mechanisms in general (Hunt & Brouillette, 1987).

(a)   Brainstem Studies

During the past decade investigations have concentrated on verifying or disproving the apnea theory of Sudden Infant Death Syndrome by studying the anatomic sites of ventilatory control: the brainstem and the carotid body, and the organs generally affected by chronic hypoxia, the brain, pulmonary vasculature, liver, adrenal glands and brown fat (Kelly & Shannon, 1982).

Possible brainstem mechanisms producing apnea include failure of:-

-        Essential neuronal populations and pathways associated with the generation of breathing rhythm.
-        Sensory (chemoreceptive, proprioceptive, or irritant) inputs to these sites.
-        Neurotransmission to the respiratory muscles of the thorax and/or upper airway, and
-        Arousal pathways to wake the infant and terminate sleep apnea and avoid irreversible hypoxic damage (Kinney and Filiano,1988).

Brainstem mechanisms generating a terminal cardiac arrythmia include an imbalance of sympathetic and parasympathetic control of the heart, or neurally mediated prolongation of the QT interval (Schwartz, 1987).

Numerous studies have concentrated on the brainstem, documenting increased astrocyte gliosis, particularly in the area of the watershed zone of the brainstem circulation which is located in the region of the nuclei that regulate autonomic function (Naeye, 1976; Takashima, Armstrong, et al, 1978). Astrocytes are supporting cells in the central nervous system whose resting function are not fully known. As a result of injury, astrocytes react with an increase in size and number. The rapid reproduction of reactive astrocytes is known as gliosis. It is assumed to be a non-specific response to central nervous system insult after the second trimester, and accompanies essentially all metabolic,

34

toxic, infectious, and other damage. Gliosis occurs mainly in reaction to neuronal injury and indicates the site of neuronal loss. Summers and Parker (1981) in a retrospective investigation of brainstem morphology in 34 Sudden Infant Death Syndrome Infants revealed medullary gliosis in the reticular formation in 12% of Sudden Infant Death Syndrome victims. Astroglial proliferation and delayed myelinization in the medulla (Naeye, & Drake, 1975), in addition to ischemic cell changes, (Leech & Alford, 1977), and scattered perivascular fat-laden cells (Gadsdon & Emery, (1976) have also been described. Naeye (1974) feels that these changes are secondary to the chronic hypoxemia thought to be experienced by the Sudden Infant Death Syndrome victim. Guntheroth (1973) has indicated that moderate hypoxia may be associated with apnea in Sudden Infant Death Syndrome victims. Reports of impaired post-natal growth (Peterson, Benson, et al, 1974), increased pulmonary arterial muscle (Naeye 1973), brown fat retention, extramedullary haematoporesis, (Naeye, 1976) and perivascular fat laden cells (Gadsdon & Emery, 1976) in the central nervous system seem to suggest that these infants may suffer from a state of chronic hypoxemia.

Studies in primates have indicated that asphyxia will alter the histology of this area, causing possible dysfunction (Myers, 1973). Total perinatal asphyxia for more than 10-15 minutes results in a typical pattern of brain damage which always involves brainstem structures. By contrast, partial asphyxia left much less permanent damage. Nyke (1976) contrasted hypoxemia due to toxaemia present during the last trimester of pregnancy with asphyxia at birth. Only early hypoxia caused brainstem damage in humans. He related his findings to the rate of cell division and the resulting large energy demand of maturing cells in the brainstem. The brainstem astroglial proliferation described in a number of Sudden Infant Death Syndrome cases is probably not a result of asphyxia at birth, but more likely the result of hypoxic stimulus initiated earlier during pregnancy and maintained for a longer time (Hoppenbrouwes & Hodgman, 1982).

Thus the gliosis seen in Sudden Infant Death Syndrome victims in the brainstem involving the nucleus ambiguous, dorsal motor nucleus of the vagus, and the nucleus of the solitary tract, may be the result of hypoxia, and may thus result in abnormal regulation of breathing. Cole et al (1979), found smaller glomic cells and fewer chemoreceptor granules in the carotid body, in 6 Sudden Infant Death Syndrome victims when compared with the controls. Naeye et al (1976) described reduced glomic volume in 63% of Sudden Infant Death Syndrome victims. These victims manifested no evidence of chronic hypoxia and increased glomic volume in 23% of Sudden Infant Death Syndrome cases with hypertrophy of the pulmonary vasculature. The abnormalities of the carotid body are, however, not yet fully understood. An unconfirmed study on the cervical vagus reports a reduction in the number of small myelinated fibres (Sachis, Armstrong et al, 1981). Thus abnormalities in the anatomic structures that control

breathing in Sudden Infant Death Syndrome victims is reported by several researchers. The cause of these changes is unknown, however, animal studies of the brainstem indicate the possibility of hypoxia-ischemia (Myers, 1975).

However, not all sites are always involved in the studies reported. One study reported gliosis in the dorsal motor nucleus of the vagus and midline and paramedian regions of the medulla (Takashima, Armstrong, et al, 1978), whereas the study by Kinney et al (1983) did not. In all of the studies reported, the astrocytes counted are qualitatively indistinguishable between Sudden Infant Death Syndrome and control groups. Furthermore, reactive astrocytes have not been counted volumetrically, but rather in a single cross-sectional area (Kinney & Filiano, 1988). Neuronal and astrocytic populations are not divided equally in brainstem nuclei and the shapes of brainstem nuclei change at different levels and with age (Summers & Parker, 1981). Brainstem gliosis appears to be prevalent in some, but not all, Sudden Infant Death Syndrome victims. This may indicate a subset of Sudden Infant Death Syndrome infants with primary brainstem injury as a result of unknown, non-hypoxic insult or a subset with recurrent apnea and secondary injury as a result of chronic hypoxia. Gilles et al, (1979) suggested infantile atlanto-occipital instability as a potential mechanism of brainstem ischemia and sudden death due to bilateral vertebral artery decompression.

Tissue that could be altered by chronic hypoxia has been examined by some researchers. Investigations of the smooth muscle of the pulmonary vasculature have shown this to be increased in infants dying of Sudden Infant Death Syndrome, and in infants with cyanotic heart disease (Williams, Hawter & Reid, 1979), and recently near Sudden Infant Death Syndrome victims who subsequently died of Sudden Infant Death Syndrome (Williams, Shannon, et al, 1980) However, the findings of further studies has been conflicting (Naeye, 1973). Other pathologic studies suggest further changes in autopsies of infants with chronic hypoxia and in Sudden Infant Death Syndrome victims involving increased periadrenal brown fat (Naeye, Whalen, et al, 1976), depletion of the adrenal medulla (Naeye, 1976), hepatic erythropoiesis (Naeye, 1974), increased fat cells in the cerebral spinal fluid, fatty metamorphosis in the area of the tapetum (Gadsdon & Emery, 1976), and failure of regression of the reticulodendritic spines in the reticular formation (Quattrochi, Baba, et al, 1980). Takashima and Becker (1985) investigated dendritic development and gliosis in the medullary magnocellular reticular nucleus and solitary and dorsal vagal nuclei.

Developmental delay of the normal diminution of dendritic spines was found in the magnocellular reticular nucleus and/or vagal nuclei of a significant proportion of Sudden Infant Death Syndrome infants. This delayed neuronal maturation of dendritic spines indicates immature neural respiratory

control mechanisms in Sudden Infant Death Syndrome. This may imply a physiological immaturity with a greater tendency towards apnea and secondary hypoxic damage to the brainstem. Astrogliosis in the brainstem has been reported in both the reticular formation (Gadsdon & Emery, 1976) and particular nuclear groups (Kinney, Burger et al, 1983). Astrogliosis is a marker of reactive change in astrocytes and as such indicates scarring. These changes could be due to hypoxia and/or ischemia. The selective vulnerability to hypoxia-ischemic injury of the neonatal and infantile brainstem, including the tegmentum, with the ventral and dorsal respiratory groups, is well recognized and offers further supporting evidence (Schneider, Ballowitz, et al, 1975). Takashima and Becker (1984) suggest that the persistence of reticular dendritic spines may indicate a structural abnormality characteristic of Sudden Infant Death Syndrome and abnormal or immature neural respiratory control in Sudden Infant Death Syndrome infants. The respiratory control of Sudden Infant Death Syndrome infants may represent a persistence of immature respiration.

The above overview of causal and physiological and biochemical factors implicated in Sudden Infant Death Syndrome shows quite clearly that a specific etiology has not been established. Even the central hypothesis, that of Sudden Infant Death Syndrome being the consequence of apnea-related morphological change and ultimate death has not received unambiguous support. Therefore, there has not been sufficient evidence to support a single common pathway in the causation and mechanism of Sudden Infant Death Syndrome.

What has been established, however, is that a significant proportion of Sudden Infant Death Syndrome infants show some, albeit subtle, neurophysiological damage or neurochemical dysfunction. Therefore, although a common cause, or even grouping of causes has not been effected, and a final common pathway in the form of a specific pathogenesis has not been described there is compelling evidence of subtle neurophysiological and neurochemical deficits in Sudden Infant Death Syndrome. Because of this, it is entirely logical and acceptable that the diverse studies in the field appears somewhat piecemeal, lacking a centralized theory, or even paradigm for studying, understanding, or explaining, the Sudden Infant Death Syndrome phenomenon. In this regard, it parallels the situation in schizophrenia theory and research. Furthermore, numerous references in Rie and Rie (1980) compared "the state-of-the-art" theory and research in schizophrenia to another neurodevelopmental phenomenon, Attention Deficit Hyperactivity Disorder.

2.1.9   Neural Control of Cardiorespiration and Arousal

Breathing is a complex motor act which depends on numerous extensive central nervous system sites,

from the cerebral cortex to spinal cord (Euler, 1983). Therefore the genesis and regulation of breathing is not the result of simple reflexes united by a single brainstem respiratory centre, but includes a group of control systems hierarchically organized to fulfil changing metabolic requirements (Euler, 1983). Rostral sites, amygdala, and the hypothalamus, exert significant regulatory roles upon brainstem and spinal cord areas, specifically during waking. The rhythmic drive to breathe originates in the medulla. The specific neurotransmitters of respiratory control are many and incompletely understood (Lagercrantz, 1987). They include "fast-switching" neuro-transmitters like acetylcholine, amino acids and monoamines (Lagercrantz, 1987).

The hypoxic inhibition of respiration observed in very young infants, appears to be a vestige of strong hypoxic respiratory depression in the fetus (Lagercrantz, 1987). The efferent limb of respiration includes the nucleus of the tractus solitarius in the medulla and the sensory division of the vagul complex. The efferent limb of respiration includes the premotor neurons in the medulla that project to the spinal cord motor neurons. Auditory brainstem evoked potential measures the brainstem auditory pathways located in the rostral medulla, pons and midbrain, and therefore do not assess cardiorespiratory circuits directly, so their value in defining dysfunctions is limited (Kinney & Filiano, 1988).

Central cardiac control includes parasympathetic and sympathetic pathways (Natelson, 1985). The dorsal vagal nucleus and nucleus ambiguous in the medulla comprises the parasympathetic motor efferent system: these axons descend to the heart. The principle neurotransmitters involved in cardiac control are norepenephrine, acetylcholine and serotonin (Natelson, 1985). Arousal involves the neural pathways originating in the reticular formation of the rostral pons, midbrain and hypothalamus. There are also dispersed and widespread cortical projections in the serotonergic raphe nuclei in the rostral pons and midbrain and from the noradrenergic locus coeruleus in the rostral pons. The neurotransmitters which mediate arousal are not fully understood: acetylcholine, norepinephrine, serotonin, and dopamine have been investigated. There is a great deal of circumstantial evidence which indicates that many Sudden Infant Death Syndrome victims die because of failure of the respiratory system. Many may stop breathing or may not be able to resume breathing during sleep. The most important defence mechanism of the respiratory system which protects an infant from hypoxia or apnea is to awake. Arousal from sleep is a logical defence mechanism. Infants at extremely high risk for Sudden Infant Death syndrome, with severe unexplained apnea, were tested. Keens (1989) found that only 40% off these infants aroused normally. Therefore, 60% failed to arouse in response to allow oxygen challenge (Keens, 1989). This implies that these infants lack normal defence mechanisms which protect them from low oxygen during sleep.

Research is now concentrating on the cause of the abnormal hypoxic arousal response. Possibly, the part of the brain which controls sleep and wakefulness or the part of the brain which contains arousal, is abnormal (Keens, 1989). If this is the explanation then infants with an abnormal hypoxic arousal response may also have an abnormal arousal response to other sensory stimuli (Keens, 1989). Studies are presently in progress using a high risk group of infants, measuring the arousal response to light and sound. If the abnormal hypoxic response is the result of abnormalities in the regulation of sleep and wakefulness, then possibly infants at increased risk may also be unsuccessful in arousing to a bright light shining on their face, or at a loud noise during sleep, which would arouse normal infants.

Secondly the infant may be unable to detect low oxygen levels. This would be the result if these infants chronically had low oxygen in their blood. Circumstantial evidence from pathologic studies of tissue from Sudden Infant Death Syndrome victims implies that many Sudden Infant Death Syndrome victims have been chronically hypoxic before death. Van der Hal, et al (1984) found that 62% of the babies tested with apnea, failed to arouse from quiet sleep at a level of hypoxia to which all control infants aroused. In puppies, the ventilatory response to hypoxia matured with age, and this maturation was more pronounced in quiet sleep (Haddad, Gandhi, Mellins, 1982). This maturation took place during the first 10 days of life in newborn lambs (Bureau, Begin, 1982). All infants were studied beyond this age. Failure of hypoxic arousal occurred in older babies with infant apnea. This suggests that failure of hypoxic arousal was not the result of developmental immaturity. More than half the babies with apnea of infancy failed to arouse from quiet sleep in an investigation by McDullock, Brouillette & Guzzetta (1982). This indicates an abnormality in the recognition of hypoxia or in the central brainstem response to hypoxia. Sleep fragmentation and deprivation have been shown to hinder arousal responses to respiratory stimuli (Bowes, Woolf, Sullivan (1980). Therefore physical stresses that disrupt sleep, eg upper respiratory tract infection and immunizations, may further predispose these babies to a critical situation because of their arousal defects. In order to understand these interactions more closely, it would be necessary to investigate possible neurophysiological state organization in Sudden Infant Death Syndrome infants.

2.1.10   State Organization in the Sudden Infant Death Syndrome Infant

The interaction between arousal, breathing, and certain neurophysiological and neurochemical functions comprise certain functional levels, or "states", that vary in different developmental stages. It is at this level that the hypothesized apneic condition could be initiated and maintained. Sterman & Hodgman (1988) proposed, on the basis of studies of intrauterine somatic activity, that state organization begins during fetal development with the emergence at approximately 20 weeks gestational age, of a quiet-

active cycle mediated by brainstem organization. Herein definitive periodicities in the heart rate and heart rate variability in late gestation has been demonstrated, which is independent of maternal measures and coincided closely to those observed in the same infants after birth (Hoppenbrouwers, Ugartechea, et al, 1978). It is this basic cycle that accords a 60 minute periodicity to practically every physiological variable in the infant. This physiological periodicity is evidently a very early immediacy in nervous system development. The substrates for state organization are basic to development and appear to be endogenous to the maturing fetus. The early active sleep - quiet sleep cycle in the fetus is ultimately included into a sleep-waking cycle, which manifests after birth with the maturation of forebrain neuronal organization (Sterman & Hodgman, 1988).

The most obvious change in physiological arrangement during infancy was found to be the development of a sleep-waking cycle, which brought about the lengthening and redistribution of both wakefulness and quiet sleep (Sterman & Hoppenbrouwers, 1971). Thus, a circadian sleep-waking cycle became superimposed over a preserved and stabilized ultradian rest-activity cycle. This post-natal reorganization was achieved basically within the first 12 weeks of infancy. The unique regulation of the newborn period is thus replaced by a more dichotomous, forebrain-mediated wakefulness and sleep. After the maturation of an active forebrain sleep-induction system has developed, a functionally incorporated circadian sleep-waking cycle can become connected with the temporary loss of higher level maintenance. If the ensuing restriction or altered regulation of visceral functions is to have any affect on physiological deficiencies, it is at this point that such an impact might result (Sterman & Hodgman, 1988). Possibly, this accounts for the unique fact that most Sudden Infant Death Syndrome deaths occur between 2 and 4 months of age. Coons and Guilleminault (1985) investigated developmental sleep patterns in infants at known risk for "near-miss" Sudden Infant Death syndrome. They found significant differences suggestive of a temporary and subtle developmental delay. These infants retained rapid eye movement (REM) sleep at neonatal proportions, and stage two rapid eye movement sleep appeared later. Sudden Infant Death Syndrome infants have fewer movements in all sleep states than do age-matched controls. This decrease in movement may suggest a preexisting condition involving the central nervous system (Coons & Guilleminault, 1985).

The differences in sleep state distribution between aborted Sudden Infant Death Syndrome infants and normal infants share a common pathophysiologic alteration with the ventilatory and cardiac abnormalities reported by Haddad et al (1981), perhaps involving the catecholaminergic system. Harper et al (1981a) suggested that state temporal organization can be used as a sensitive assessment of development in at-risk infants. The disorganization of states in at-risk infants begins as early as the first week of life in active sleep, and continues until the sixth month of life, with reduced active sleep power

in the hourly organization of sleep (Harper, 1981a). The discovery of disturbed state organization in the first week of life, implies that the mechanisms for risk develop in fetal life, because the state differences originate before differences in maternal-infant interaction can develop (Harper, Frostig et al, 1982). Disturbances in heart-rate and variability and respiratory parameters manifesting so soon after birth would imply a disturbance in prenatal development. These sleep disturbances are still observed at 6 months. Harper et al (1981a) speculate that the operative mechanisms for Sudden Infant Death Syndrome may interact with state organization during the risk period, but further protective mechanisms develop subsequently. Monad et al (1967) illustrated three types of state disturbances in newborns with central nervous system damage:

- An absence of cycle organization.
- Alterations of the consolidations between motor, respiratory, and EEG patterns.
- Alterations of the lengths of cycles.

Thoman et al (1988) proposed an alternative hypothesis suggested by characteristics found in an infant who died of Sudden Infant Death Syndrome. The infant was part of a :normal" group of infants whose sleep and respiration patterns were being closely studied during the first post-natal weeks of life. The infant died at three months of age. Findings of a postmortem carried out on this Sudden Infant Death syndrome infant were indicative of chronic hypoxemia, as suggested by Naeye (1973). Subsequent comparison of the infant's data with those of other infants sleep and sleep-associated respiratory characteristics were noticeably different. It was revealed that the infant's state patterns were unstable. This was suggested by an unusually high occurrence of state changes within each weekly observation and unusual state patterns over successive weeks. Furthermore, the infants respiratory patterns were abnormal, showing a shortage, rather than surfeit, of brief and prolonged central apneas (Thoman et al, 1989). This combination of abnormalities is compatible with recent views which believe the pathophysiology of Sudden Infant Death Syndrome to be more complex than an abnormality restricted to respiratory control (Hoppenbrouwers & Hodgman, 1982; Shannon & Kelly, 1982; Valdes-Dapena, 1980; Kelly et al, 1989). Sudden Infant Death Syndrome is now regarded as a congenital condition, which involves generalized central nervous system vulnerability. An infant's states are a sensitive indicator of functioning in widely distributed regulatory systems in the central nervous system (Kelly & Shannon, 1979; Hobson et al, 1986; Thoman et al, 1989).

Inconsistency in state organization over the early weeks was the antecedent condition for later dysfunction or subsequent death. Developmental inconsistency in state organization during the neonatal period is predictive of risk for later development Thoman, Denneberg et al, 1981; Tynan, 1986;

41

Prechtl, Theorell, Blair, 1973). Extremely low levels of respiratory pauses are considered to be an indication of chronic mild hypoxemia (Hoppenbrouwers & Hodgman, 1982). Obviously, unusually low frequencies of brief apnea are a form of respiratory abnormality. This observation is not unusual as extremes in either direction are acknowledged as pathological for many biological functions, including heart-rate blood pressure and temperature (Thoman et al, 1989). Research findings have specified characteristics including sex, premature birth, being a sibling of a Sudden Infant Death Syndrome infant, or certain neurobehavioural parameters that generally indicate an increased probability of Sudden Infant Death Syndrome with any group of infants (Thoman et al, 1989). Furthermore, Hoppenbrouwers et al, (1980), reported that subsequent siblings of Sudden Infant Death Syndrome infants exhibited transient accelerated maturation of the circadian pattern which could be indicative of a physiological deficit which may be manifestations of a compensatory response to an oxygen deficit which would influence neurobehavioural parameters.

2.1.11 Accelerated Maturation Hypothesis

In essence, the accelerated maturation hypothesis holds that elevated thyroid hormone levels during the perinatal period resulted in accelerated cortical neuronal maturation, with resultant premature development of both EEG and behavioural patterns response (Shapiro, 1971). Therefore, the elevated thyroid hormone levels in Sudden Infant Death Syndrome victims provides a possible explanation for the abnormalities mentioned above (Tildon, Chacon, 1983). Increased metabolic activity may account for elevated respiratory and heart-rates while the resulting acceleration of forebrain maturation would further advance a more rapid state development. This concept is referred to the "accelerated maturation hypothesis" of Sudden Infant Death Syndrome. However, Haddad et al, (1981) arrived at a conflicting conclusion. They observed a significant reduction in quiet sleep time at three months of age in "near-miss" Sudden Infant Death Syndrome infants when compared to controls. They ascribed this observation to a delayed maturation of sleep. The consolidation of sleep into right time hours and a related reduction of sleep during the day are classical signs of sleep-state maturation (Kleitman, 1963).

Guilleminault and Coons (1983) also suggested that state maturation was delayed in "near-miss" infants. Sterman and Hodgman (1988) propose that the early maturation of neural substrates for sleep and waking could result in a higher threshold for arousal at a critical period in autonomic regulatory maturation. Their data suggest that a relevant decrease in central arousal threshold during sleep accompanies the functional progression represented by the post-natal adaptation period of infant development. Speculation is that maturational sequencing contributes a temporary facilitation of central nervous system arousal mechanisms to accommodate the gradual suppression of autonomic functions

associated with the maturation of a fore-brain-mediated sleep process. When the brain-stem mechanisms, which are slow to mature have caught up with this process, arousal thresholds return to previous levels (Sterman & Hodgman, 1988). The more rapid maturation of both processes results in a developmental mismatch with lowered arousal threshold occurring prior to the completion of the post-natal adaption period.

Therefore, a sleep-mediated restraint or deregulation of brainstem autonomic functions, which is still pronounced between 2 and 4 months, is not compensated by an increased potential for arousal. Under these circumstances the infant would be especially susceptible to any influence that either promoted the depth or duration of quiet sleep or added further stress to an already compromised autonomic regulation (Sterman & Hodgman, 1988). A useful research direction might be to concentrate on mechanisms of state transitions and on disturbances of systems which alter state composition (Ryan & Megirian, 1982).

2.1.12 Subsequent Siblings

Sudden Infant Death Syndrome is not considered to be genetically determined. However, repeated Sudden Infant Death Syndrome events have been reported in a family, (Steinschneider, 1972) and recent data indicate that the risk of Sudden Infant Death Syndrome is increased 3:6 to tenfold, in subsequent siblings of Sudden Infant Death Syndrome victims (Irgens, Skjaerven et al, 1984). The pathophysiology resulting in repeated deaths in some families is unknown, and the role played by genetic and environmental factors, or pre-or postnatal factors is still to be debated. A higher risk of repetition in the next sibling than in all subsequent siblings is expected because the total pattern of risk factors will be more similar in the next sibling than in siblings born later (Peterson et al, 1986). These risk factors would include the fact that Sudden Infant Death Syndrome infants and siblings share an intrauterine environment that is not too dissimilar with time lapse. Only Peterson (1986) compared the Sudden Infant Death Syndrome rate for subsequent siblings of Sudden Infant Death Syndrome victims, to a properly matched control group.

When compared with controls matched for maternal age, birth order etc., the Sudden Infant Death Syndrome rate for siblings was not significantly higher than the rate for these matched controls. Peterson et al, (1985) concluded that earlier estimates of Sudden Infant Death Syndrome siblings risk to Sudden Infant Death Syndrome were based on research that was biased and thus inflated. Although Peterson et al, (1985) found that the Sudden Infant Death Syndrome sibling risk is almost four times that of the Sudden Infant Death Syndrome risk among births generally, it is possible that this comparison is confounded by the combined effects of maternal age and birth order. Furthermore, when

Sudden Infant Death Syndrome occurrences among Sudden Infant Death Syndrome family cohort siblings were compared with maternal age and birth order matched control family cohort siblings, there was no statistically significant difference in Sudden Infant Death Syndrome rates, or in total infant mortality rates. He reported that siblings of Sudden Infant Death Syndrome victims are not at high risk for Sudden Infant Death Syndrome, or infant death from other causes to any significant degree. Peterson et al (1985) maintained that from his data, it appears that earlier estimates of the risk of Sudden Infant Death Syndrome in siblings were inflated.

If the Sudden Infant Death Syndrome rate is elevated in subsequent siblings of Sudden Infant Death Syndrome victims, does this fact imply that Sudden Infant Death Syndrome is inherited?

An increased familial incidence may be the result of environmental factors, be genetically inherited, or be coincidental. A family may remain in the same environment for the birth of several children. Therefore, environmental factors may cause an increased occurrence of a disorder among siblings in that family. Furthermore, infants born to the same mother experience similar intrauterine environments. This is particularly true for twins, who have a high risk for Sudden Infant Death syndrome (Peterson, Chinn et al, 1980). It has not been possible to clearly distinguish heredity from environment as the cause of increased familial incidence (Peterson, Chinn et al, 1980). However, twin studies have been used to make this distinction. The Sudden Infant Death Syndrome rate is noticeably increased in the surviving twin sibling of a Sudden Infant Death Syndrome victim (Beal, 1983). However, the incidence remains the same whether the twins are monozygotic (identical; share the same genetic inheritance) or dizygotic (fraternal; have different genetic inheritance). If Sudden Infant Death Syndrome is genetically inherited, one would expect the incidence to be higher amongst identical than fraternal twins. This is not the case (Peterson 1980). Thus, in general, it appears that Sudden Infant Death Syndrome is not inherited but is more likely to be environmental, either pre- or postnatal in origin.

Studies of the recurrent Sudden Infant Death Syndrome risk do reveal Sudden Infant Death Syndrome rates above that of the general population for subsequent siblings of Sudden Infant Death Syndrome victims (Davidson-Ward, Keens et al, 1986). What is the possible explanation for this increased Sudden Infant Death Syndrome rate? Firstly, all Sudden Infant Death Syndrome siblings share a moderately increased risk for Sudden Infant Death Syndrome) Peterson, Chinn et al, 1980). This implies that these infants share similar characteristics, and that the causes of Sudden Infant Death Syndrome in all families are similar. Secondly, that most Sudden Infant Death Syndrome siblings have no increased risk. Possibly, a small group of Sudden Infant Death Syndrome victims may have had causes which have a high familial pattern. This would suggest that the causes of Sudden Infant Death Syndrome are

44

multifactorial which may differ among families exhibiting different risks. This second hypothesis would predict that certain subsets of Sudden Infant Death Syndrome siblings exist who are at extremely high risk.

In families who have one or more previous Sudden Infant Death Syndrome victims, subsequent siblings appear to be at increased risk (Oren, 1987). Half-siblings of two previous Sudden Infant Death syndrome victims seem to share the same risk, which appears to strengthen the environmental hypothesis. Infants with one previous Sudden Infant Death Syndrome victim and apnea of infancy may have severe apneic episodes, but no deaths were detected (Oren, Kelly & Shapiro, 1987). However, closer examination of specific issues present in Sudden Infant Death Syndrome siblings appear important at this point in time.

The hypothesis involved in this investigation is that anoxia results in brain damage. Pasamanick and Knobloch (1966) have postulated a "continuum of reproductive casualty" as resulting from complications of the peri-natal period. This continuum may be represented by death at the extreme end, and by a "syndrome of minimal cerebral damage" at the other extreme. It is this latter group which is more difficult ti identify. It appears from investigation of the literature, reviewed above, that Sudden Infant Death Syndrome infants are a subgroup affected in a possibly similar manner.

While it is not possible to "prove" that small degrees of anoxia will produce damage in humans, such a demonstration has been made using lower animals. Windle (1963) demonstrated that a period of asphyxia in Macaca Mulatto monkeys which does not require resuscitation, may still produce discrete brain lesions. No resulting behavioural deficits could be measured. Still further support is provided by Towbin's work, demonstrating neuropathological changes in infants and adults for whom anoxia was likely and either pre- or perinatally. The problem here is, however, that unlike the case in Attention Deficit Hyperactivity Disorder, neuropsychological assessment of the manifest disease is impossible, as death is the fullest manifestation of the condition.

Recent research would suggest that the difference between brain damaged and normal children in some areas of functioning will be apparent at all ages, some at earlier, but not later ages, and some will not be apparent in early childhood, but can be demonstrated in later childhood or adolescence (Teuber & Rudel, 1962). Many of the symptoms of organic brain damage, such as irritability, hyperactivity, and impulsiveness, appear to diminish as the child matures. Hebb (1949) suggested that early brain damage would affect learning structures in the brain which would retard development in this areas. However, if one considers that the one or more genetic or intrauterine variables that contributes to the

development of the manifold causes of Sudden Infant Death Syndrome would also affect *siblings of the* Sudden Infant Death Syndrome infant, the possibility of testing Sudden Infant Death Syndrome siblings for neuropsychological deficits associated with these anomalies arises. This would then include the possibility that, *given the broad similarities in sub-clinical brain damage leading to neuropsychological anomalies,* that Sudden Infant Death Syndrome infants, Sudden Infant Death Syndrome siblings, or children with Attention Deficit Hyperactivity, Attention Deficit Disorder, or Tourette's Syndrome, might show similar neuropsychological problems. The correlation between potentially relevant factors, eg. sex, status, familial preference, pre- and perinatal complications, minor physical anomalies, response to medication, neurological "soft" signs, and developmental precursors, and immaturity (Taylor & Fletcher, 1983) appear to support a causal relationship between Attention Deficit Hyperactivity Disorder, Attention Deficit Disorder, Tourette's Syndrome, and Sudden Infant Death Syndrome siblings.

(1)   Specific Characteristics of Sudden Infant Death Syndrome Siblings

Oren et al (1986) noted that Sudden Infant Death Syndrome siblings who experienced one apparent life-threatening event have a distinctly increased risk of dying from Sudden Infant Death Syndrome. They found that infants who had an apparent life-threatening event that required full resuscitation and were siblings of a Sudden infant Death Syndrome victim, have a   25% mortality rate. The combination of severe apnea and a family history of Sudden Infant Death Syndrome marks a high risk group of infants. Kelly et al (1982) found a significant increase in the incidence of apneas of 5 to 9.9 seconds and 10 to 14.9 seconds in subsequent Sudden Infant Death Syndrome siblings when compared to controls. It is possible that the increase in short apnea in siblings may cause desaturation, or it may simply be a predecessor, in some infants, to prolonged apnea or hypoventilation. The incidence of abnormalities in ventilatory control and response to hypoxia and hypercarbia in Sudden Infant Death Syndrome siblings is much greater than the incidence of death in this group (Kelly, Twanmoh et al, 1982). These changes may be the result of basic physiologic defect coupled with environmental factors triggering decompensation. It is possible the a physiologic or pathologic abnormality in the mother could result in an hypoxic intrauterine environment. This could lead to a pathologic condition in the brainstem eventually causing abnormal ventilatory control.

Hoppenbrouwers et al (1980), observed that during the first 3 months of life, a pattern in respiratory rates emerged which appeared to be the nightly portion of a circadian rhythm. Subsequent siblings of Sudden Infant Death Syndrome infants exhibited transient accelerated maturation of this circadian pattern. During the first month of life, minima in respiratory rates in quiet sleep occurred during the

second and third intervals of the night in subsequent siblings, a pattern not observed in control infants until 3 months of age. Gluck et al, (1977) demonstrated an accelerated pattern of lung development by as much as 8 weeks early in intrauterine growth-retarded fetuses. Minkowsky (1978) presented data of increased levels of neurotransmitters, eg. serotonin and precursors in fetal rats with experimentally induced intrauterine malnutrition. Hoppenbrouwers et al (1980) speculate that accelerated maturation in electroencephalic sleep frequencies and respiratory circadian patterns in subsequent siblings of Sudden Infant Death Syndrome infants are manifestations of a compensatory response to oxygen deficit.

Although the risk of dying of Sudden infant death syndrome is merely 2% for the subsequent siblings, this is actually a ten fold increase in risk compared to the general population (Froggat, Lynas & MacKenzie, 1979). Infants are the most vulnerable between 6 and 12 weeks of age (Beckwith, 1973). The majority of infants die during normal sleeping hours and are generally seen alive at the last feeding before the parent's bedtime (Valdes-Dapena, 1988). Autopsy reports have identified the morning hours shortly before normal waking as the most likely time of death (Bergman, Beckwith & Ray, 1970). A circadian pattern in heart rate and temperature emerges at 6 weeks of age and coincides with the vulnerable age for Sudden Infant Death Syndrome (Beckwith, 1973). Hoppenbrouwers et al (1980) demonstrated the emergence of a circadian pattern in respiratory rates during the first 6 months of life in normal full-term infants. The pattern was characterized by decreased respiratory rates between approximately 10.00 pm and 04.00 am. Subsequent research demonstrated that respiratory rates in subsequent siblings were constantly higher than those from control infants during the above times (Hoppenbrouwers, Hodgman et al, 1977). Naeye (1974) demonstrated pathologic changes in Sudden Infant Death Syndrome infants, that is suggestive of chronic hypoxia preceding death. Increased respiratory rates in subsequent siblings are a possible compensation for mild chronic hypoxia.

This concept is supported by a study of infants known to be hypoxemic, who manifested accelerated respiratory rates during quiet sleep (Bruck, Adams, et al, 1962). Successful compensatory behaviour may be distinctive of the majority of infants at high risk for Sudden Infant Death Syndrome. Assuming that increased respiratory rates are a response to hypoxia in siblings, can the accelerated maturation of the circadian pattern be another compensatory response.

Investigators reported distinct developmental differences between subsequent siblings of Sudden Infant Death Syndrome infants and normal infants with respect to heart rate and heart rate variability as a function of age and sleep-waking status. The risk group had a higher heart rate at 3 months of age, particularly when awake. Their heart rate increased more markedly during the first month of life in both quiet sleep and active sleep. The heart rate for both groups declined after 2 months in every state, but

the risk infants lagged in this regard. In the awake state, heart rate variability in the risk group did not follow the increase seen among control infants during the 1 week to 2 months age period (Harper, Leake, et al, 1978). These authors concluded that there are distinct developmental differences between subsequent siblings of Sudden Infant Death Syndrome infants and control infants with respect to heart rate and its variability. These differences may reflect delayed maturation or impaired function of the autonomic nervous system and particularly of vagal control (Valdes-Dapena, 1980). However, some of the differences may be suggestive of chronic hypoxia. Thus, they submit both chronic hypoxia and the dysfunction of autonomic control which might result from it, could play a critical function in Sudden Infant Death Syndrome (Valdes-Dapena, 1980).

Five of seven Sudden Infant Death Syndrome siblings examined by Korobkin and Guilleminault (1979) had abnormal neurologic examinations in infancy with findings similar to Sudden Infant Death Syndrome victims. Central nervous system damage suggested by certain authors prior to the terminal episode is manifested in abnormal limb hypotonia and prolonged depression of the state of consciousness. One may speculate that the hypotonia and "near-miss" event may both be expressions of intrinsic central nervous system abnormalities in certain "near-miss" infants. Another subpopulation of infants may develop progressive neurologic disability because of repeated apnea. Thus, the group of infants labelled high risk for Sudden Infant Death Syndrome appears to be at risk for later neurodevelopmental abnormalities. Thoman et al, (1988) in her studies with siblings of Sudden Infant Death Syndrome victims reported abnormalities in respiratory function and sleep-wake characteristics from the first days after birth. Respiration in both sleep states was characterized by extremely low frequencies of brief apneic pauses, a deficiency of prolonged apneas, and an absence of periodic respiration, while the state organization was extremely unstable over weeks and the states were temporally fragmented within observations. These same neurobehavioural characteristics were observed in an earlier Sudden Infant Death Syndrome infant (Thoman, Miano et al, 1977, 1988).

These neurobehavioural characteristics conform with the growing acknowledgement that infants who are at risk for Sudden Infant Death Syndrome or prolonged apneic episodes may have a subtle central nervous system dysfunction present from birth (Weinstein & Steinschneider, 1985; Anderson-Huntington & Rosenblith, 1976; Korobkin & Guilleminault, 1979; Naeye et al, 1976: Navelet, Payan et al, 1984). Therefore, the current general consensus appears to be that the neural regulatory dysfunction associated with Sudden Infant Death Syndrome is generalized and involves more than just respiratory control. Recent evidence indicates that risk infants may have already been challenged in utero, and that environmental pollutants may contribute to functional hypoxia (Hoppenbrouwers, Calab, et al, 1980). Such minor aberrant stimuli in pre- and postnatal life may trigger compensatory

physiologic responses or aggravate existing minor abnormalities. While these adjustments might be initially adaptive, when prolonged, they might initiate a sequence of events which maintains, rather than limits abnormal functioning. Increased respiratory rates represent such an adaptive response. The majority of infants would be presumed to compensate successfully with little or no clinical symptomatology. The accumulation of minor abnormalities, or the episode of a sudden stress may present a challenge for which the infant can no longer compensate. Identification of compensatory responses, are conceivably useful in explaining underlying mechanisms. These mechanisms remain unproven, but the possibilities include cardiac arrhythmias, prolonged apnea from central respiratory control failure, and seizure induced apnea. Epidemiological studies have shown that a sub-optimal intrauterine environment is present to excess in future victims (Southall, 1988).

Several paths of research appear to be converging towards a better understanding of a problem that has long confounded investigators. They include research on sleep apnea and its effects on heart rhythm, on respiratory reflexes, state stability, and pathological changes in Sudden Infant Death Syndrome victims. There is also a concerted effort to apply this information to devise tests that will predict infants at risk for Sudden Infant Death Syndrome. The differences between subsequent siblings and controls may explain mechanisms placing an infant at increased risk.

(2)   Implication of Neurological Lesions in Siblings

Studies by Harper et al (1981) demonstrate that subsequent siblings of Sudden Infant Death Syndrome victims have decreased spontaneous arousals from sleep. Thus Sudden Infant Death Syndrome siblings appear to have an abnormality in their hypoxic arousal response compared to controls. This dysfunction could result in the infant becoming hypoxic, the severity of the disorder depending on the severity of the abnormality (Van der Hal, Rodriques, et al, 1985). Research has shown that hypoxia results in neuropathological lesions and/or subtle central nervous system abnormality (Brand & Bignami, 1969; Korobkin & Guilleminault, 1979). The areas in which the brain lesions are found in infants dying from Sudden Infant Death Syndrome corresponds with that found in premature infants who are a high risk group for Attention Deficit Hyperactivity Disorder (Fuller et al, 1983). Therefore, siblings of Sudden Infant Death Syndrome victims who exhibit similar symptoms could possibly be a high risk group for the same disorder.

When the siblings central nervous system is exposed to perinatal complications, the lesions may or may not be immediately symptomatic or fatal. Thus there may be subclinical lesions which may result in little or no subsequent clinical evidence of central nervous system damage in survivors (Fuller et al,

1983). The associated implications of a potential gradation in the degree of neural loss, whether focal, multifocal, or diffuse, in the hippocampus, corpus callosum, cerebellum, cerebral cortex, or deep cerebral nuclei (basal ganglia and thalamus areas) are suggestive of many hypotheses about the possible relationships between the lesions and abnormal learning and behaviour (Fuller et al, 1983). The graded degree of neuropathological changes observed suggests that similar degrees of damage might have occurred in siblings who survived Sudden Infant Death Syndrome.

Leech and Alford (1974) have presented evidence that perinatal leucoencephalopathy (white matter damage) is one of several precursors of the syndrome, Attention Deficit Hyperactivity Disorder. Recently, Fuller et al, (1983) found extensive gray matter necrosis in sites where it had been thought not to occur, and which could be considered as further possible evidence for the occurrence of Attention Deficit Hyperactivity Disorder. These lesions have been found in Sudden Infant Death Syndrome victims and subclinical cerebral lesions in the subsequent sibling often remain latent (Towbin, 1971). Borderline central nervous system impairment may be responsible for behavioural disorders often accompanied by learning defects, reading disability, hyperactivity, and motor disturbances, or abnormal neurologic findings and electroencephalographic irregularities. The processes of hypoxic cerebral damage are not of an all-or none character, Lesser hypoxic lesions occurring in the fetal-neonatal period are correspondingly responsible for the appearance later of lesser patterns of clinical disability, for varied subtle forms of attenuated, distorted central nervous system function (Rosen, 1969). Scholtz, (1956) has emphasized that a depletion of cells up to thirty percent in the brain, although inconspicuous anatomically, may be associated with significant disability. In the term fetus and neonate with protracted exposure to hypoxia, the cortex may develop focal, patchy devastation. In infants surviving, the damaged cortical tissue is replaced by gliosis, resulting in areas of scarring and contraction (Towbin, 1971).

Thoman et al (1988) maintained that the neural regulatory dysfunction associated with Sudden Infant Death Syndrome is generalized and involves more than just respiratory controls. State stability has already been found to be affected by subtle central nervous system dysfunction (Thoman, Davis et al, 1988).

The hippocampus, which is particularly vulnerable to hypoxia, is an essential part of the limbic system, which is generally acknowledged as being involved in the regulation of emotions and activity levels (Fuller, Guthrie et al, 1983). The detection of necrosis and lipid-laden cells in the hippocampus in association with neonatal hypocapnic insults and central nervous system haemorrhage strongly implies that hippocampal damage associated with neonatal complications can occur in neonates through cerebral

ischemia (Lee, Grassi et al, 1979). The hippocampus is also deemed to be the generator of Pavlovian internal inhibition necessary in quieting to a stimulus (Douglas, 1975). Furthermore, the hippocampus is involved in memory consolidation (Milner & Penfield, 1955)., emotion (Papez, 1937), error evaluation (Douglas & Pribram, 1966), loss of response suppression (Douglas & Isaacson, 1964), and perseveration (Kimble & Kimble, 1965). Milner et al (1968) maintain that the hippocampus is particularly involved in the translation of short-term to long-term memory (Fuller, Guthrie, Alford, 1983).

The cerebellar lesions are of concern when studied in association with the generally found "soft" neurological signs; lack of fine and gross motor control, clumsiness, and difficulty in balance and visual-motor control (Fuller et al, 1983). The identification of necrosis, haemorrhage and lipid-laden cells in the cerebellar deep nuclei and white matter with neonatal asphyxia and hypoxemia in infants who died from Sudden Infant Death Syndrome demonstrates that these lesions can occur following neonatal complications and may have functional significance in those infants who survived these obstacles (Takashima, Armstrong, Becker, et al, 1977).

The potential outcome of varying degrees of lesions in the corpus callosum and the lateral ventricles (Gadsdon & Emery, 1975), are interesting. Impulses arriving from all areas of the cerebral cortex by way of the association and commissural fibres terminate generally in the second and third layers of the various cortical areas. The term "disconnection syndrome" is applied to the effects of lesions of association pathways. The brains of Sudden Infant Death Syndrome infants autopsied commonly manifested subcortical leukomalacia. The cerebral white matter is particularly vulnerable in the infant brain (Gadsdon & Emery, 1975). Periventricular leukomalacia, a lesion described by Banker and Larrouche, (1962) is located generally in the deep white matter. These white matter lesions occur primarily in the neonatal period and are generally associated with a respiratory condition that compromises the quality and quantity of cerebral circulation (Takashima, Armstrong et al, 1978). As Ford (1966) has indicated, many cases of minor insult to the central nervous system with mild impairment of neurologic function go unrecognized. Focusing upon this consideration, concerned with borderline central nervous system impairment, is the Attention Deficit Hyperactivity Syndrome. This syndrome describes the large group of infants, children, and adolescents, who have behavioural disorders often accompanied by learning defects, reading disability, hyperactivity, and motor disturbances described as inordinate awkwardness, or abnormal neurologic findings and electroencephalographic irregularities (Towbin, 1971).

2.2.13   Conclusion

It is abundantly clear that research into Sudden Infant Death Syndrome has shown that no single mechanism explains all sudden infant death. As the neuroanatomical and neurochemical substrate of cardiorespiratory control and arousal are extremely complex, there may be several neural mechanisms of Sudden Infant Death Syndrome as well,which may involve different or combined sites in the appropriate pathways. Furthermore, brainstem mechanisms may play a subordinate role, as explained in a recent hypothesis in which the putative primary defect occurs in lung surfactant, but cholinergic pathways are implicated in producing prolonged apnea (Talbert, Southall, 1985). However, to explain the unique age distribution of Sudden Infant Death Syndrome, there must be a critical biochemical or molecular event in central nervous system maturation, which occurs at 2-4 postnatal months and which includes a final common pathway in neuronal energy metabolism or neurotransmission upon which many insults act to produce sudden death. If such an age-dependent pathway could be discovered, the inter-relationship between various factors associated with Sudden Infant Death Syndrome may be explained. Therefore, overwhelming challenges in brainstem research are to identify potential neurological subsets in the total Sudden Infant Death Syndrome population, explain the primary or secondary role of brainstem mechanisms and, most significant, establish the assumed age-dependent final common pathway for brainstem-mediated sudden death (Kinney & Filiano, 1988).

The most formidable challenge is to find the cause of brainstem lesions and ascertain their causal relationship to sudden death through animal studies. These lesions should be investigated without the constraints of the cardiorespiratory hypothesis. Kinney et al (1988) reported gliosis in the inferior olivary nucleus, which is a major cerebellar relay nucleus; although olivary-cerebellar circuits are not directly involved in respiratory rhythm generation or drive, cerebellar effects upon autonomic control has been described experimentally. One could hypothesize that olivary lesions in Sudden Infant Death syndrome lead to primary autonomic dysfunction, or that chronic hypoxia is the cause, based on the analogy to their presence in infants with cardiac or pulmonary disease (Rourke, 1982).

What does however, emerge from the present state of knowledge is that there exists some neurological substrata that could be causally related to Sudden Infant Death Syndrome, and that this relates through a yet not fully known mechanism to sleep apneic causation of further neurological damage and subsequent death. As noted earlier in this paper, Attention Deficit Hyperactivity Disorder reflects a similar final common pathway grouping of symptoms with diverse, but neurologically substrated causes of the disorder. It is well known that a variety of disabilities may underlie Attention Deficit Hyperactivity Disorder. It has become evident that the syndrome is not a homogeneous clinical entity.

Attempts to identify subgroups within the population of Attention Deficit Hyperactivity Disorder children, have steadily increased. For several decades, biological factors have been viewed as major contributors to a variety of specific behavioural and learning problems. The most often mentioned argument in favour of central nervous system factors is the supposed similarity between Attention Deficit Hyperactivity Disorder, and those thought to accompany brain damage in children. But, in general, the behavioural sequelae of definitive brain injury do not seem to be mirrored in Attention Deficit Hyperactivity Disorder (Fletcher & Taylor, 1989).

Attention Deficit Hyperactivity Disorder as a developmental disorder (Stander, 1988) shows many parallels to Sudden Infant Death Syndrome. As in the case of Sudden Infant Death Syndrome, Attention Deficit Hyperactivity Disorder also seems to show a confusing variety of neurophysiological and neurochemical factors in its etiology, also without a central theory or paradigm to account for the observed variances in the plethora of associated research findings. In addition, Attention Deficit Hyperactivity Disorder also manifests in "soft" neuropsychological symptoms - as does Sudden Infant Death Syndrome. Recent developments in paradigmatic neuropsychology (Reynolds et al, 1989) have, however, shown that a neuropsychologically-based paradigm could be used to account for the diversity of findings in research on Attention Deficit Hyperactivity Disorder, leading to greatly improved understanding, prevention, and treatment of Attention Deficit Hyperactivity Disorder (Reynolds et al, 1980).

In this regard, it might be entirely possible that the Sudden Infant Death Syndrome phenomenon could be explained in a neuropsychological context, not dissimilar to Attention Deficit Hyperactivity Disorder. Before such an undertaking can be made, however, it would be advantageous to investigate the neuropsychological correlates of Attention Deficit Hyperactivity Disorder as a basis for explanatory undertakings of Sudden Infant Death Syndrome. The characteristics manifested in infants later to be diagnosed as having Attention Deficit Hyperactivity Disorder are similar to those manifested in Sudden Infant Death Syndrome victims and siblings. These findings are consistent with the notion of subtle central nervous system dysfunction in Sudden Infant Death Syndrome risk infants from the time of birth. It appears therefore, that Sudden Infant Death Syndrome infants share many symptoms with their siblings, and that the possibility exists that a less lethal variant of this condition's central mechanism exists in the siblings of Sudden Infant death Syndrome (Oren et al, 1987). These symptoms, often manifest as "soft" neurological or neuropsychological anomalies, showing a large degree of correspondence with those symptoms often found in Attention Deficit Hyperactivity Disorder. It is therefore possible that Sudden Infant Death Syndrome not only shows significant overlap with Attention Deficit Hyperactivity Disorder, but manifests symptoms found in other neuropsychological disorders,

such as Attention Deficit Disorder and Tourette's Syndrome, as there appears to be considerable overlap in the symptoms manifested by children diagnosed as suffering from these disorders.

Sudden Infant Death Syndrome could therefore share a broadly defined generalized neuropsychological risk factor with these disorders. It is also possible that in being sub-categories of a postulated "generalized neuropsychological risk condition", and showing some degree of inheritability, it is necessary to look more closely at the clinical signs present in these disorders, as a background against which the symptoms and mechanisms of Sudden Infant Death Syndrome might be viewed.

2.2   Attention Deficit Hyperactivity Disorder

2.2.1   Introduction

Attention Deficit Hyperactivity Disorder represents the diagnostic classification designed to provide a more precise description of children who in the past may have been diagnosed by such terms as Minimal Brain Dysfunction or the Hyperactive Child Syndrome (Shaywitz, Shaywitz, Jatlow et al, 1990). It is estimated that 2% - 5% of school age children suffer from some form of attention deficit disorder (Rostain, 1991). The most widely used definition of attention deficit disorders is provided by the Diagnostic and Statistical Manual (DSM 111-R) of the American Psychiatric Association, which provides two diagnostic categories: Attention Deficit Hyperactivity Disorder (ADHD) and Undifferentiated Attention Deficit Disorder (ADD). Attention Deficit Hyperactivity Disorder represents one of the most frequently diagnosed neurobehavioural disorders in children., affecting perhaps as many as 20% of the school-going population. Symptoms of Attention Deficit Hyperactivity Disorder, although subtle, are at the same time pervasive, influencing every aspect of a child's life - his home, school, and relationships with peers (Rostain,1991).

Evidence from a number of investigative groups suggests a substantial overlap between Attention Deficit Hyperactivity Disorder and Learning Disabilities. The prevalence of Learning Disabilities in Attention Deficit Hyperactivity Disorder is estimated to be 9-10% in hyperactive boys (Halperin et al, 1984). Conversely, the prevalence of hyperactivity in learning disabled populations has varied from 41% (Holborrow & Berry, 1986) to 85% (Safer & Allen, 1976), with a prevalence of 33% reported in an epidemiological sample. Studies examining the academic achievement of hyperactive, compared to control children, support the idea that significantly more Attention Deficit Hyperactivity Disorder children experience academic achievement problems (Cantwell, 1978).

54

2.2.2   Definition of Attention Deficit Hyperactivity Disorder

The term Attention Deficit Hyperactivity Disorder is used as a medical designation for certain aberrations of behaviour and/or cognitive functioning, resulting from milder forms of central nervous system dysfunction or developmental deviation (Clements & Peters, 1987). The term refers to children of near average, average or above average general intelligence with certain learning and/or behavioural disabilities ranging from mild to

TABLE 2.1

DSM-111-R Diagnostic Criteria for Attention Deficit Hyperactivity Disorder

A disturbance of at least 6 months during which at least eight of the following are present:

Often fidgets with hands or feet or squirms in seat (in adolescents, may be limited to subjective feelings of restlessness)

Has difficulty remaining seated when required to do so

Is easily distracted by extraneous stimuli

Has difficulty awaiting turn in games or group situations

Often blurts out answers to questions before they have been completed

Has difficulty following through on instructions from others (not caused by oppositional behaviour or failure of comprehension), e. g. fails to finish chores

Has difficulty sustaining attention in tasks or play activities

Often shifts from one uncompleted task to another

Has difficulty playing quietly

Often talks excessively

Often interrupts or intrudes on others, e.g. butts into other children,s games

Often does not seem to listen to what is being said to him

Often loses things necessary for tasks or activities at school or at home (e.g. toys, pencils, books)

Often engages in physically dangerous activities without considering possible consequences (not for purpose of thrill - seeking), e.g. runs into street without looking

Onset before 7 years old

Not caused by pervasive development disorder

severe, which are associated with deviations of function of the central nervous system. These deviations may manifest themselves by various combinations of impairment in perception, conceptualization, language, memory, and control of attention, impulse or motor function (Rostain, 1991). These aberrations may arise from genetic variations, biochemical irregularities, perinatal brain insults, or other illnesses or injuries sustained during the period which is critical for the development and maturation of the central nervous system, or from unknown causes. These central nervous system alterations may be permanent, and manifest during the school years as a variety of learning disabilities (Clements & Peters, 1981).

2.2.3   Definition of Attention Deficit Disorder

Historically, the antecedents of the current controversy surrounding the relationship between Attention Deficit Disorder and Learning Disability can be traced to the late nineteenth-early twentieth century. Various researchers extrapolated the concept of brain damage to include children with behaviours similar to those observed after known brain injuries (Shaywitz & Shaywitz, 1991). However, Clements and Peters (1962) elaborated on the notion of minimal brain dysfunction which, in their view, could be inferred from the presence of a cluster of symptoms including specific learning deficits, hyperkinesis, impulsivity and short attention span and confirmed by findings on examination of "equivocal" neurological signs and a borderline abnormal or a definitely abnormal EEG.

Attention Deficit Disorder is a residual category for disturbances in which the predominant feature is a persistence of developmentally inappropriate and marked inattention that is not a symptom of another disorder, such as mental retardation or Attention Deficit Hyperactivity Disorder, or of a disorganized and chaotic environment (Shaywitz & Shaywitz, 1992).

Publication of DSM-111 in 1980 marked a watershed in the evolution of Attention Deficit Disorder as specific exclusion and inclusion criteria were established for the disorder. However, the current difficulties originated when two subtypes of Attention Deficit Disorder were noted based on the presence or absence of symptoms of hyperactivity: attention deficit disorder with hyperactivity and attention deficit disorder without hyperactivity. DSM 111 was unclear whether "they are two forms of a single disorder or represent two distinct disorders"(APA, 1980, p. 41).

Publication of DSM-111-R in 1987 represented a distinct change and further added to the confusion by blurring the distinction between attention disorder with and without hyperactivity by focusing primarily on ADDH, now termed Attention Deficit Hyperactivity Disorder, and relegating ADDnoH to a

57

category now termed Undifferentiated Attention Disorder. According to Barkley, Costello and Spitzer (in press) this step was taken because it was felt that ADDnoH might actually "represent a type of inattention believed to accompany the non-verbal learning disabilities (Rourke, 1989) and thus might be a new subtype of the existing category of Specific Developmental Disorders".

2.2.4   Subtypes of Attention Deficit Disorder

Strong evidence supports this differentiation between subtypes of attention disorder, demonstrating that while Attention Deficit Disorder Hyperactivity and Attention Deficit Disorder no Hyperactivity do not differ on independent measures of attention (King & Young, 1982; Edelbrock et al, 1984; Lahey et al, 1987) Attention Deficit Disorder Hyperactivity and Attention Deficit Disorder no Hyperactivity children demonstrate significantly different behavioural, academic and social patterns (Edelbrock et al, 1984). Of particular interest, Lahey et al (1987) indicate that Attention Deficit Disorder boys are rated by their teachers as manifesting a poorer school performance compared to Attention Deficit Hyperactivity Disorder boys, a finding supported by the high rate of retention, 71%. It has been found that symptoms cluster into two domains: inattention - disorganization (ADD) and hyperactive - impulsive (ADHD), and provide still further support for the construct of Attention Deficit Disorder without hyperactivity (Lahey et al, 1988).

Studies indicating that children manifesting inattention but not hyperactivity may represent a high risk group for school failure demand that the occurrence of such an attentional subtype be investigated , and if validated, definitional guidelines for its diagnosis be provided. The data of Berry et al, (1985) indicate that girls with Attention Deficit Disorder are less likely to be hyperactive and also less likely to be diagnosed although they demonstrate significant attentional, cognitive and language deficits. Thus children with Attention Deficit Disorder no Hyperactivity may represent an underidentified group of children who are at significant risk for long-term academic, social and emotional difficulties.

Recent advances in neuroimaging, neurophysiology, and neurochemistry have provided significant new insights into the mechanisms responsible for Attention Deficit Disorder and Learning Disabilities. Learning Disability, primarily reflecting reading disability, is related to abnormalities in language centres in the brain (Rostain, 1991). Attentional mechanisms appear to be located in frontal brain regions, although a posterior attentional centre is present as well.

2.2.5   Clinical Features

Children diagnosed as suffering from Attention Deficit Hyperactivity Disorder generally have a disorder in one or more of the basic psychological processes involved in understanding or using language, written or spoken. It appears that there are many children who exhibit differing degrees of deviations in learning and behaviour. It is suspected that these deviations arise from subtle dysfunctioning or developmental variations within the central nervous system. The early identification of the disorder is important in order for the individual to achieve the potential of which he is capable (Clements & Peters, 1981). The following signs and symptoms are descriptive of Attention Deficit Hyperactivity Disorder, although every individual will not manifest every symptom:

- Specific disabilities in learning,
- Deficits in attention,
- Deficits in receptive, integrative and/or expressive language,
- Deficits in memory,
- Abnormality in motor activity level,
- Deficits in coordination and other soft neurologic signs,
- Deficits in perception (auditory, visual, and/or proprioceptive,
- Deficits in comprehending abstractions at various levels,
- Lability of emotion,
- Impulsivity. (Clements & Peters, 1981).

The child manifesting hyperkinesis appears to be in constant motion, or may be merely restless and fidgety. It may also manifest as voluble uninhibited speech, or as disorganized, even in the absence of outward hyperkinesis (Rostain, 1991). Often the child is unable to concentrate for very long on one activity. He especially loses interest when abstract material is presented. Some children may exhibit good attention span when their interest is aroused, but when not so engaged, display severe distractibility to causal stimuli. Often these children exhibit "soft" neurological signs, such as mixed and confused laterality, slow speech development, and general awkwardness (Clements & Peters, 1983).

2.2.6   Pathophysiology

The pathophysiology of Attention Deficit Hyperactivity Disorder and Attention Deficit Disorder is not known as present, although evidence for a neurobiologic mechanism is accumulating, the specific brain processes involved remain undetermined (Rapoport, Ferguson, 1982: Shaywitz & Shaywitz, 1984). The most likely neuroanatomic lesion in Attention Deficit Hyperactivity Disorder and Attention Deficit Disorder is the frontal lobe, anterior and medial to the precentral motor cortex. Xenon cerebral blood

flow studies of patients with Attention Deficit Hyperactivity Disorder and Attention Deficit Disorder have found central hypoperfusion of the frontal lobe and decreased blood flow to the caudate nucleus (Rostain, 1991). Methylphenidate increases blood flow to the basal ganglia and decreases flow to frontal or motoric regions. There is some evidence for a decreased turnover of dopamine and for a supersensitivity to released dopamine in Attention Deficit Hyperactivity Disorder and Attention Deficit Disorder patients (Zametkin, Nordahl, et al, 1991). Pharmacologic studies with dopamine agonists, however, fail to demonstrate a primary deficiency of dopamine.

The most significant pharmacologic effect on Attention Deficit Hyperactivity Disorder and Attention Deficit Disorder symptoms have been found with stimulants such as methylphenidate and dextroamphetamine, both of which work on catecholamine and dopamine metabolism, lending strong support to the role of both in this disorder (Zametkin & Rapaport, 1987). In view of the inconsistent findings from neurotransmitter studies, it appears that Attention Deficit Hyperactivity Disorder and Attention Deficit Disorder involve both complex neuroanatomic and neurochemical alterations in function.

The majority of psychophysiological studies have measured peripheral autonomic arousal, but there is a growing interest in investigation into cortical measures, and there is growing support for the hypothesis of central nervous system under-arousal for at least a sub-group of hyperactive children (Yellin, 1978; Ferguson & Pappas, 1979). Although evidence for neurobiologic mechanisms is accumulating, the specific brain processes involved remain undetermined (Rapoport, & Ferguson, 1982; Shaywitz & Shaywitz, 1984). The most likely neuroanatomic lesion in Attention Deficit Hyperactivity Disorder and Attention Deficit Disorder is the frontal lobe, anterior and medial to the precentral motor cortex (Chelune, Ferguson et al, 1986; Mattes, 1980).

(1)   Frontal lobe involvement

Although evidence for neurobiologic mechanisms is accumulating, the specific brain processes involved remain undetermined (Rapoport, Ferguson, 1982; Shaywitz & Shaywitz, 1984), the underlying neuroanatomical and/or neurophysiological mechanisms of the disorder remain unclear (Trites, Laprade, 1983). Early studies focusing on the hyperkinetic aspect of Attention Deficit Hyperactivity Disorder posited an underlying defect in central nervous system arousal systems. Lanfer, Denhoff & Solomons (1957) suggested that hyperactivity resulted from cortical "overarousal" due to a diencephalic (thalamic and/or hypothalamic) deficit.

Initially, Connors, Eisenberg & Sharpe (1964) observed that Attention Deficit Hyperactivity Disorder children appeared to lack inhibitory capacity over their internal drives and responses to external stimuli. Dykman et al (1971) suggested that a defect in an hypothesized forebrain inhibitory system would account for Attention Deficit Hyperactivity Disorder, on the basis of deficient inhibition of reticular and diencephalic structures through its descending pathways.

With the recent shift in emphasis from the hyperkinetic to attentional components of Attention Deficit Hyperactivity Disorder, the role of higher cortical inhibitory mechanisms have become of interest. It has been suggested that a defect in a hypothesized forebrain inhibitory system would account for Attention Deficit Hyperactivity Disorder and Attention Deficit Disorder on the basis of deficient inhibition of reticular and diencephalic structures through its descending pathways (Chelune, Ferguson et al, 1986). Mattes (1980) has drawn a striking parallel between frontal lobe dysfunction and the symptoms of Attention Deficit Hyperactivity Disorder. While deficient frontal lobe functioning may not account for all forms of Attention Deficit Hyperactivity Disorder and Attention Deficit Disorder, the frontal lobe hypothesis does offer a parsimonious model for explaining many of the findings associated with Attention Deficit Hyperactivity Disorder and Attention Deficit Disorder. The prefrontal regions of the frontal lobes have a rich network of reciprocal pathways with the reticular formation and the diencephalic structures (Fuster, 1980), which regulate arousal and the ability to suppress responses to task irrelevant stimuli (Grueninger & Grueninger, 1973).

Lesions of the prefrontal regions result in a breakdown of the regulation of goal-directed activity and modulation of impulsive responding (Luria, 1973; Numan, 1978). Patients with such lesions have difficulty suppressing ongoing activities despite environmental feedback that they are no longer appropriate (perseveration) and demonstrate increased reactivity to extraneous stimuli (distractibility and impulsivity), which results in deficient goal-directed behaviour (Benson, Stuss, 1982; Drewe, 1975; Gorenstein, 1982; Milner, 1963; Petrides, Milner, 1982). Hyperactivity is also among the behavioural sequelae associated with frontal lobe lesions (Hecean & Albert, 1976). Hyperactivity is thought to be the result of disturbed higher levels of cortical inhibition in the form of a failure of inappropriate responses, disinhibition of inhibitory cortical reflexes, or an absence of inhibition of orienting responses that therefore become stronger (Konorski, 1967). Given the apparent similarity in the behavioural manifestations of Attention Deficit Hyperactivity Disorder and Attention Deficit Disorder, and adult patients with frontal lobe disorders, it is tempting to infer, by analogy, a common central nervous system origin. However, since clear central nervous system deviations have not been established in Attention Deficit Hyperactivity Disorder and Attention Deficit Disorder, a different approach to independent assessment must be taken (Fletcher & Taylor, 1984). One such approach is to examine the

behavioural/cognitive correlates of the manifest disorder (Chelune et al, 1986).

Assessment of the frontal lobe hypothesis of Attention Deficit Hyperactivity Disorder from a neuropsychological perspective has been hampered by controversy and speculation as to when the behaviours attributed to frontal lobe functioning reach functional maturity. According to Luria (1973), the prefrontal regions do not begin to get ready for action until the child is between the ages of 4-7 years, while Golden,(1981) has suggested that the frontal regions do not become functionally mature until adolescence. The question of developmental change is relevant to understanding the nature of Attention Deficit Hyperactivity Disorder since it is essentially defined as a disorder of maturation; the cognitive and behavioural abilities of the Attention Deficit Hyperactivity Disorder and Attention Deficit Disorder child are not regarded as deviant, but rather as developmentally inappropriate for the child's chronological age (Chelune et al, 1986).

Alabiso (1982) suggests that Attention Deficit Hyperactivity Disorder and Attention Deficit Disorder may have an underlying dysfunction of the inhibitory forebrain system controlling attentional processes in response to situational demands. Generally, Attention Deficit Hyperactivity Disorder and Attention Deficit Disorder is viewed as a maturational lag, although this hypothesis is not unchallenged (Calloway, Halliday et al, 1983) This hypothesis is derived from the clinical observation that Attention Deficit Hyperactivity Disorder children appear to behave in a manner that is younger than their peers, and that some of the aspects of the disorder diminish with increasing age (Konorski, 1967). Electrophysiological data supporting the view that arousal levels in Attention Deficit Hyperactivity Disorder and Attention Deficit Disorder children tend to become normalised with age have been offered by Satterfield & Braley, 1977). Furthermore, electroencephalographic studies of Attention Deficit Hyperactive Disorder and Attention Deficit Disorder patients demonstrate abnormal evoked potentials, particularly in response to novel stimuli presented to the subject after habituation (Connors, 1990). Satterfield (1973) found that hyperactive children had significantly smaller evoked potentials than controls. He reported that the evoked potential components noted in the study may reflect neural activity in two different functional systems, one concerned with attentional mechanisms, and with the processing of incoming auditory information, the other with the central nervous system arousal. Disturbances in both attentional and arousal systems have been implicated in the hyperactive child's pathophysiology (Douglas, 1972; Satterfield et al, 1974). Similarly, Rapoport & Ferguson (1981) report "that at the complex level of cortical evoked potentials, the difference between hyperactive and normal children appears to be attributable to variations in maturational level" (p.673).

(2)   Poorly modulated level of activity

A study of psychophysiological variables has reflected attempts to test "arousal" hypotheses which have been proposed as the organic basis of hyperactivity. The motor restlessness, attention problems, and other performance deficits shown by these children, are all amenable to explanations involving hypothetical central nervous system arousal systems (Douglas, 1979). These hypotheses have been of two types: over-arousal and under-arousal. Over-arousal could result either directly from excitatory processes or indirectly from under-active inhibitory processes (Wender, 1971; Buckley, 1972). Under-arousal hypotheses implicate underactive excitatory processes. The latter proposals represent an especially attractive theoretical position since they could explain both the behavioural symptoms and the seemingly paradoxical response of hyperactive children to stimulant drugs. Data supports the hypothesis of central nervous system under-arousal for at least a subgroup of Attention Deficit Hyperactivity Disorder children. Distractibility and inattentiveness seem to be related to the high level of activation. Anxious, hypomanic and manic adults - all of which may be described as overactive, manifest attentional changes similar to those seen in Attention Deficit Hyperactivity disorder; the inability to fixate attention for long periods, forgetfulness and increased distractibility (Rosenthal & Allen, 1978). A significant percentage of Sudden Infant Death Syndrome siblings manifested similar increased activation (Rie & Rie, 1981).

2.2.7   Genetic transmission

Evidence of a biological basis for Attention Deficit Hyperactivity Disorder might come from a study of relatives of Attention Deficit Hyperactivity Disorder children, to see if there is a consistent pattern of disorders associated with this syndrome, or if these disorders "breed true" (Morrison & Stewart, 1971), A possible relationship between Attention Deficit Hyperactivity Disorder and Attention Deficit Disorder and alcoholism may exist, as it was found that a higher proportion of fathers and mothers of hyperactive children were alcoholics compared with controls. A later study showed that adoptive parents of hyperactive children did not have a higher prevalence of alcoholism, hysteria or sociopathy (Cantwell, 1972). However, increased rates for alcoholism, sociopathy and hysteria in the parents of Attention Deficit Hyperactivity Disorder or Attention Deficit Disorder children were found, suggesting genetic transmission of a general impulsive-antisocial-hyperactive syndrome in these male offspring.

Several studies have provided evidence that Attention Deficit Hyperactivity Disorder and Attention Deficit Disorder may be transmitted within families. Twin and adoption studies suggest that this familial clustering may be due to genetic factors (Goodwin, 1975). Analyses of data support the hypothesis that

63

there is a strong familial clustering for Attention Deficit Hyperactivity Disorder and Attention Deficit Disorder. The observed patterns suggest that vertical transmission of the disorder occurs and that the sex difference observed in the population prevalence might be explained by a threshold effect. Logistic analyses indicate that a model that includes sex of the proband, parental affected status, and maternal positive family history as independent variables, most adequately explains the patterns in the families (Pauls et al, 1991).

2.2.8   Interaction of Etiological Factors

(1)   Pre- and Perinatal Risk Factors

Congenital risk factors are often cited as providing support for the notion of a biologically based hyperkinetic syndrome (Rapoport & Ferguson, 1981). The relationship appears to be non-specific with regard to behavioural profile. Pasamanick and Knobloch (1960) suggested that prenatal and perinatal risk factors, such as bleeding in pregnancy, or low birth-weight, showed significant relationships with learning and behavioural problems, when the child was of school age. There appears to be a group of vulnerable children, whose environment may not compensate for insults during the prenatal period, and these insults are expressed in a variety of ways. Nichols and Chen (1981) obtained factor scores for academic achievement, hyperactivity, neurological problems, and immaturity, from age seven. Some associations between behavioural and neurological scores were found, and prenatal variables had some predictive relationship. It was noted that maternal smoking or proteinuria during pregnancy had some relationship to hyperactivity, low academic achievement, or neurological soft signs. Thus prenatal and perinatal measures support the complex, multivariate notion of risk in association with diverse psychopathology.

(2)   Minor Physical Anomalies

An association between the number of minor physical anomalies and behaviour or learning problems originating in early childhood, has been found. An association between the number of minor physical anomalies of hands, feet, head, ears, face, and mouth, and behaviour or learning problems originating in early childhood (Waldrop et al, 1986; Waldrop & Halverson, 1971; Quinn & Rapoport, 1974). It was found that hyperactive boys with high anomaly scores, were more likely to have had an early onset of hyperactivity than were the hyperactive boys in the same study who had a total score of three or less for these anomalies (Quinn & Rapoport, 1974). A genotype-phenotype model was proposed to account for the various factors that are known to influence the formation of these features in the first trimester

of fetal development of minor anomalies in populations of hyperactive children has been replicated by Firestone (1976, 1978) and other workers have found a higher incidence of anomalies for other behaviourally deviant paediatric populations (Walker, 1977, Campbell et al, 1978; Links et al, 1978). These studies suggest that, at least for males, there is a congenital contribution to these types of behaviour. An association between high anomaly scores and some types of "difficult" behaviour was found for both males and females (Rapoport & Ferguson, 1981). The relationship between a measure of congenital developmental deviation and problem behaviour is interesting. A general spectrum of difficulties is validated including learning disabilities (Campbell et al, 1978). Waldrop et al, (1978) have found, for males, significant correlations between anomalies and hyperactivity, distractibility, and conduct problems (O'Donnell & Van Tunran, 1979; O'Donnell et al, 1979).

These studies suggest a congenital contribution to these types of behaviour, at least for males. High anomaly male infants were more likely to have difficulty getting along with their peers, and to be considered hyperactive and distractible, than were low anomaly infants. Several studies have shown an increased frequency of minor anomalies in learning-disabled and autistic children (Steg & Rapoport, 1975; Walker, 1977; Campbell et al, 1978).

(3)   Neurological Soft Signs

Soft neurological signs have been found to be useful in diagnosing Attention Deficit Hyperactivity Disorder. Unfortunately. the value of soft signs seems limited. Some studies have shown that there is a slightly greater total number of neurological soft signs among hyperkinetic children, others have not (Cap et al, 1977; Werry et al, 1972:; Werry and Anon, 1976). Others have found them to be associated with behavioural disturbance in only a non-specific way (Mikkelsen et al, 1981). Involuntary movements, cerebellar functioning, and parietal lobe activity are referred to as the "soft" signs of Attention Deficit Hyperactivity Disorder. Although these are not pathognomonic for Attention Deficit Hyperactivity Disorder, they can be viewed as markers of neurodevelopmental delay. The child's speech and receptive language abilities are important to screen in so far as communication disorders and learning disabilities can be present in children with Attention Deficit Hyperactivity Disorders.

A study of psychophysiological variables has reflected attempts to test "arousal" hypotheses which have been proposed as the organic basis of hyperactivity. The motor restlessness, attention problems, and other performance deficits shown by these children (Douglas & Peters, 1979) are all sympathetic to explanations involving hypothetical arousal systems. These explanations imply neurological locus, but follow the premise that current arousal level is a function of the state of activity in the juxtaposed

excitatory types: over-arousal and under-arousal. The latter proposal represents an especially attractive theoretical position since it could explain the behaviour symptoms and the response of hyperactive children to stimulant drug therapy (Werry, 1090; Satterfield et al, 1974a). Over arousal could result either directly from excitatory processes or indirectly from under-active inhibitory processes (Wender, 1971; Buckley, 1972). Under-arousal hypotheses implicate underactive excitatory processes.

The latter proposals represent an especially attractive theoretical position since they could explain both the behavioural symptoms and the seemingly paradoxical response of hyperactive children to stimulant drugs. Data supports the hypothesis of Central Nervous System under-arousal for at least a subgroup of Attention Deficit Hyperactivity Disorder children. Distractibility, and inattentiveness seem to be related to the high level of activation. Anxious, hypomanic and manic adults - all of which may be described as overactive, manifest attentional changes similar to those seen in Attention Deficit Hyperactivity Disorder and Attention Deficit Disorder; the inability to fixate attention for long periods, forgetfulness and increased distractibility (Rosenthal & Allen, 1978). A significant percentage of Sudden Infant Death Syndrome siblings manifested similar increased activation (Rie & Rie, 1981). Another aspect of poor modulation of activity is the tendency of some Attention Deficit Hyperactivity Disorder and Attention Deficit Disorder children to sleep either restlessly or particularly heavily. This is of particular interest because of the significant percentage of enuresis found in Attention Deficit Hyperactivity Disorder and Attention Deficit Disorder children. Studies of sleep patterns in enuretics, many of whom are presumably Attention Deficit Hyperactivity Disorder or Attention Deficit Disorder children, have shown that they may have "disorders of arousal". A series of studies by Harper, Leake et al, (1981) demonstrated that subsequent siblings of Sudden Infant Death Syndrome victims have decreased spontaneous arousals during sleep.

The neurochemical evidence for Attention Deficit Hyperactivity Disorder and Attention Deficit Disorder is contradictory at best. Urine, serum, and cerebrospinal fluid metabolites of serotonin, norepirephrine and dopamine, are not consistently different in Attention Deficit Hyperactivity Disorder and Attention Deficit Disorder patients, as compared with matched controls. Dopamine, beta-hydroxylase, monamine oxidase, and catechol-o-methyl transference are also similar in these two groups. There is some evidence of a decreased turnover of dopamine and for a supersensitivity to released dopamine in Attention Deficit Hyperactivity Disorder patients. Attention Deficit Hyperactivity Disorder symptoms have been found with stimulants such as methylphenidate and dextroamphetamine both of which work on cathecholomine and dopamine metabolism, lending some support to the role of both in this disorder. As a result of the inconsistent findings from neurotransmitter studies, neuroanatomic and neurochemical alterations in function. Zametkin and Rapoport (1987) in the review of the neurobiology of Attention

Deficit Hyperactivity Disorder conclude; "In experimental animal models, selective depletion of brain dopamine results in performance deficits with hyperactivity, while selective reduction of no epinephrine results in performance deficits without hyperactivity". Such findings suggest that alterations in particular catecholaminergic systems might differentiate between Attention Deficit Hyperactivity Disorder and Attention Deficit Disorder. Therefore, separate neural mechanisms may be responsible for each disorder (Shaywitz, Bennett, et al, 1991).

Attention Deficit Disorders are associated with a variety of other childhood psychiatric problems and numerous psychiatric conditions can present as attention difficulties. Co-morbidity has become an important age of research in recent years, as studies reveal that high percentages of children with Attention Deficit Hyperactivity Disorder or Attention Deficit Disorder also suffer from other disturbances.

Figure 2.1 graphically depicts the overlap of Attention Deficit Hyperactivity Disorder and Attention Deficit Disorder with other childhood disorders, including learning disabilities, oppositional defiant behaviour, aggressive behaviour, mood disorders (particularly depression) anxiety disorders, and among adolescents, and young adults, substance abuse and personality disorders (Rostain, 1991).

2.2.9   Neuropsychological Correlates of Attention Deficit Hyperactivity Disorder

Attention Deficit Hyperactivity Disorder is a behavioural concept with neurological implications. It must be labelled a "behavioural" concept because it is defined by specific behavioural characteristics, rather than by, as is generally the case in adult patients, by infrabehavioural evidence of cerebral abnormalities (Benton 1987). A patient can have obviously evident disease of the brain without manifesting any functional, including behavioural abnormality, as disclosed by current methods of investigation. A child cannot have Attention Deficit Hyperactivity Disorder without manifesting behavioural abnormalities.

Reitan and Boll (1980) maintain that selected behavioural deficiencies of brain damaged children have been described in the literature for many years, but only recently have extensive comparisons of normal and brain damaged children been performed. These studies have provided a background of identification, in children with known brain lesions, of behavioural deficits across a wide range of psychological functions. The problem posed is to what extent children with Attention Deficit Hyperactivity Disorder show deficits similar to those of brain damaged children as compared with performances of normal children, and also possibly Sudden Infant Death Syndrome infants and Tourette's Syndrome Sufferers.
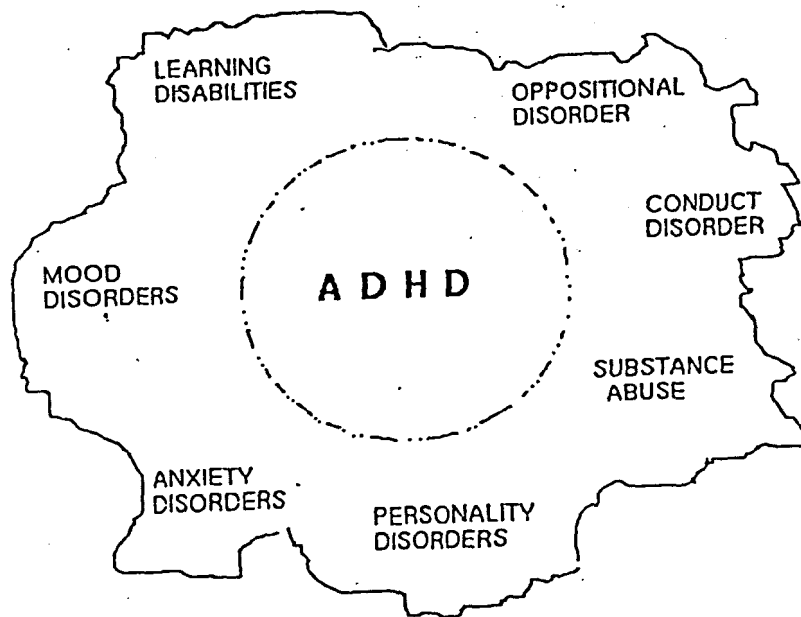
FIGURE 2.1: Co-morbidity and the elusive boundaries of attention deficit hyperactivity disorder (ADHD).

In order to understand this, however, it is necessary to investigate the vicissitudes of neuropsychological and neurological continuity in brain damage and normality.

2.2.10 Continuum Concepts

Pasamanick and Knobloch (1966) postulated a "continuum of reproductive casualty", in which the effects of damage to the brain during the pre-natal period and birth were thought to vary according to the extent of the damage. When the damage is severe, well defined neurological disorders result, but when it is mild, there is an inclination to behavioural difficulties, which are not accompanied by any overt symptoms of neurological abnormality. Pasaminick and Knobloch (1966) thus proposed the existence of "minimal brain injury",which is similar in kind, but not degree, to that which causes cerebral palsy and mental retardation. This view sees brain damage in quantitative terms as a unitary continuous variable that results in a characteristic set of deficits, the nature of which depends on the amount of brain damage suffered. The arguments for this view of Attention Deficit Hyperactivity Disorder were expressed by Gross and Wilson (1974) who maintain: The most compelling evidence for the existence of Minimal Brain Dysfunction as an entity is:

- the similarity between its symptoms and symptoms of children with proven brain disease and,
- the remarkable response to certain medications, a response not found in non Minimal Brain Dysfunction children." (p.6)

In this context it is important to examine more closely the neurological and behavioural correlates and consequences in non-overt brain damage or "subclinical" brain damage.

2.2.11 Subclinical Brain Damage

(1) Brain Damage without Neurological Abnormalities

The view of a continuum concept raises the issue whether there can be sub-clinical brain damage that results in behavioural or cognitive sequelae. Rutter (1980) maintains that it is possible for overt and indisputable brain damage to occur and yet for a careful clinical neurological examination to reveal no definite abnormalities. Solomon and associates (1963) observed that children who had distinct neurological abnormalities as infants, may appear normal when examined some years later. In Shaffer and associates (1975) research with children with confirmed gross damage to the brain, only a third showed distinct neurological signs. On examination a few years later, a third manifested no signs at all

of abnormalities, dubious or definite. These studies indicate that it is possible for some children with definite brain damage to manifest no abnormalities on clinical neurological examination, but to possibly show subtle behavioural or psychological anomalies.

(2)   Psychological Sequelae of Subclinical Brain Damage

Rutter and associates (1980) studied children who had experienced a posttraumatic amnesia of not less than 1 week after a head injury, so it is reasonable to assume that some degree of brain injury resulted. The children studied were examined 2 1/4 years after the accident by an experienced neurologist. The rate of disorder in children with severe head injuries was noted to be considerably above that in control groups. Evidently, brain injury, as indicated by post-traumatic amnesia lasting more than a week can result in psychiatric abnormalities even when there are no overt neurological sequelae (Rutter, 1980). Therefore there is evidence for the existence of psychiatric disorders due to brain injuries that are subclinical to the extent that the child's general intelligence is normal and that no abnormalities emerge on a systematic neurological examination. However, one cannot necessary generalize the result to children for whom the background gives no evidence of brain injury. On the other hand, the existence of examples of subclinical psychological deficiency does indicate limited support for the concept of minimal brain dysfunction. In this regard it appears that a differential "threshold" exists for brain damage or dysfunction to manifest in neurological, psychological or no consequences at all.

(3)   Threshold for Psychological Sequelae

A better estimate of how wide the continuum concept of Minimal Brain Dysfunction is, can be acquired in two ways (Rutter, 1982). Firstly, by determining the threshold of severity of brain injury above which psychological sequelae can be observed and secondly, by examining the sequelae of possible causes of subclinical brain injury. Broad generalization would be acceptable if the threshold is low, while if it is high, only a very limited generalization would be reasonable. There exists two indicators of which psychiatric disorders may be caused by brain injury - the appearance of new disorders in children who were psychiatrically normal before an accident and a dose-response relationship between the seriousness of injury and the risk of disorder with both research strategies. There was no indication of any increased psychiatric risk with head injuries that led to posttraumatic amnesia lasting less than a week. This same issue was studied with respect to cognitive impairment - with generally the same findings. Therefore, the evidence suggested a rather higher threshold (Rutter, 1980). Benton (1973) commenting on earlier research stated that the evidence pointed to the fact that cerebral lesions in children had to be quite extensive or have specific disorganizing properties to produce significant

behavioural abnormalities. This comment further confirms that the damage must be of some severity, to manifest in overt neurological symptoms, but of a lesser severity to manifest in psychological symptoms. The question of how this second form of severity is caused needs to be addressed at this point.

(4)   Causes of Subclinical Brain Injury

If the concept of Minimal Brain Dysfunction is to be extended, and the threshold data suggest that it should not be extended too far, the etiologies of subclinical brain injury should be considered (Rutter, 1980). Apart from the easily recognizable factors such as head injury and encephalitis, perinatal hazards are another significant etiology of subclinical brain injury. Pregnancy complications and low birth weight constitute an obvious potential source of brain injury (Clement & Peters, 1981). When severe, pregnancy complications and low weight can and do, lead to cerebral palsy and mental retardation, and it seems reasonable to assume, as suggested by Pasamanick and Knoblock (1966), that in lesser degree, brain injury might result in less devastating but still significant psychological sequelae. One of the major difficulties in any evaluation of long term sequelae of perinatal brain injury is the uncertainty as to whether such injury has actually taken place (Sameroff and Chandler, 1975). This would mean that perinatal traumata can occasionally lead to psychological sequelae even when there was no overt neurological disorder.

While it is not possible to "prove" that small degrees of anoxia will produce brain damage in humans, such a demonstration has been made for lower animals (Windle, 1960, 1963). Windle (1963) demonstrated that a period of asphyxia in Macaca Mulatta monkeys which does not require resuscitation may still produce discrete brain lesions. Retrospective studies have generally demonstrated impairment as a function of anoxia (Corah, Anthony et al, 1965). However, pregnancy complications and low birth weight tend to be much more frequent in socially disadvantaged groups, so that such sequelae that to do appear may be a result of the social adversities rather than physical injury (Davis and Butler, 1972). Subclinical brain injury is often preceded by a history of a difficult pregnancy or delivery. These infants may manifest almost pure motor signs, some of which are clear-cut or "hard", such as altered deep tendon reflexes, distinct dydiakinesia and mildly dysarthric speech (Clements & Barnes, 1978). However, some of the motor signs may be subtle or "soft", such as poor stance and mild inco-ordination, cognitive function may also be effected. Emotional lability may also be apparent (Clements & Peters, 1981). A question that arises at this point in time is whether and how indications of organic brain dysfunction can be utilized in a neuropsychological approach to subclinical brain damage.

(5)   Indications of Organic Brain Dysfunction

Critics of the continuum concept have seriously questioned the criteria by means of which low organic brain dysfunction may be recognised if the clinical neurological examination is normal (Rutter, 1980). The proponents of the concept have suggested that the form of the child's behaviour is itself diagnostic on the grounds of the close similarity with the behavioural symptoms of children with proven brain disease, (Strauss, Lehtinen, 1974). Alternatively, so-called "soft" neurological signs have been used as evidence of organic brain dysfunction. Most of these pertain to immaturities in developmental functions such as language, motor co-ordination or perception (Rutter, Graham, Yule, 1970). They are considered "soft" signs because their interpretation and meaning remain somewhat uncertain, although if appropriately assessed, many can be measured with considerable accuracy (Shaffer, Shafer et al, 1983).

Computed electroencephalographic analysis indicates some advances for pathophysiologic definition of cognitive disorders, but it has the severe limitation of generally reflecting disturbances in cortical function when subcortical dysfunction may be just as significant to their pathogenesis (Duffy, Denckla et al, 1980). A significant relationship has been found between soft signs and hyperactivity. Lucas, Rodin and Simson (1965) demonstrated an association between hyperkinesis and poor co-ordination, synkinesis, choreiform movements and dysdiadochokinesia in a study leading one to conclude that a significant relationship between Sudden Infant Death Syndrome and Attention Deficit Hyperactivity Disorder exists.

Shaffer, O'Conner, Shafer and Prupis (1983) suggest that neurological "soft" signs are significant predictors of behaviour and cognitive functioning. "Soft" signs probably have many origins. In some children they may be a consequence of mild brain damage; in others, they may represent a genetically determined individual difference that may also be related to biological determinants of psychiatric disorders (Shaffer, O'Conner et al, 1983). Clearly, the postulate that there can be subclinical damage to the brain is valid. Furthermore, there is evidence that such damage may result in behavioural and cognitive sequelae. Therefore, it appears that the notion of a continuum of brain injury probably has validity, but does not necessary lead to a particular psychiatric syndrome. If a particular psychiatric syndrome cannot be used to organize certain "soft" neurological signs, such as the case of Attention Deficit Hyperactivity Disorder and possibly also Sudden Infant Death Syndrome, one would have to turn to distinct patterns of neurological impairment as an organizing principle.

(6)   Patterns of Neuropsychological Impairment

Neuropsychological deficiencies probably comprise an infrabehavioural marker (Taylor & Fletcher, 1983). As indicated there appear to be no clearly defined demarcation between neurological "soft" signs and neuropsychological impairment. However, "soft" signs primarily involve tasks of motor and sensori-motor integration while neuropsychological tests assess higher level cognitive skills. One basis for the presumption that neuropsychological deficiencies reflect constitutional factors is the "argument by analogy" (Fletcher and Taylor, 1984). If children with Attention Deficit Hyperactivity Disorder manifest deficiencies characteristic of adults with brain damage, central nervous system dysfunction is frequently inferred. Much of this research has entailed exploration of the cognitive correlates of learning disabilities (Rourke, 1973; 1988).

Not all developmental neuropsychological deficiencies have parallels in adult neuropsychopathology. Benton (1975) noted a variety of these specific cognitive impairments, which include deficiencies in visual-motor and visual-perception functioning, intersensory integration (eg. auditory-visual matching), oral speech and linguistic development and perception of sequence and orientation. Similarly, Douglas (1980) and Barkley (1981) outlined differences between hyperactive and normal children on measures of reaction time, impulsivity and planning. Hyperactive children are inclined to exhibit slower and more variable reaction time as well as more precipitous declines in performance over time: Major problems limit the interpretation of neuropsychological measures as indices of underlying central nervous system status in children. It is difficult to support the direct extrapolation of adult-originated tasks to children, especially since Attention Deficit Hyperactivity Disorder children rarely manifest strict brain damage patterns (Taylor & Fletcher, 1983). However, if neuropsychological impairment does not fully account for certain "soft" signs, then the possibility of neural mechanism involvement must be investigated.

2.2.12   Neural Mechanism Involvement

Lou and associates (1984) studied children with Attention Deficit Hyperactivity Disorder, by means of emission computed tomography. In all eleven patients, hypoperfusion was found centrally in the frontal lobes. Seven Attention Deficit Hyperactivity Disorder children had hypoperfusion of the caudate nuclei region. The occipital lobes were relatively hyperperfused. This would mean that the blood flow to these areas was greater than normal, while other areas such as the caudate nuclei received less blood flow. After methylphenidate stimulant medication, (a medication often used to control hyperactivity in children with Attention Deficit Hyperactivity Disorder), six patients showed increased blood flow in

73

the central regions, including basal ganglia and mesencephalon. Hypoperfused regions were observed in both hemispheres in all patients with dysphasia and / or Attention Deficit Hyperactivity Disorder. The hypoperfusion was generally seen centrally in the frontal lobes, anterolaterally and posterolaterally, suggesting a relationship to border areas between major arterial territories (anterior, middle and posterior cerebral arteries, thalamostriatal and cortical branches). The relative perfusion of cortical sensory and motor regions decreased in all cases. Activation studies failed to indicate the normal increase of flow in relevant cortical regions. Hypoperfusion and low metabolic activity may therefore be the result of subtle morphologic abnormalities not detectable with Computed Tomography but with significant pathogenic implications (Lou, Henriksen and Bruhn, 1984).

In Attention Deficit Hyperactivity Disorder, this interpretation is supported by the fact that axons from the dopaminergic neurons originating in the mesencephalon pass through the central frontal lobes to reach the pre-frontal cortex (Lindwall, Bjorkland, Moore, 1974), which is presumed to be involved in the regulation of attention. These dopaminergic neurons are probably activated by methylphenidate, which blocks the membrane re-uptake of dopamine. These neurons may form the anatomic basis for the interaction between the reticular formation of the brain stem and the prefrontal lobes in the regulation of attention. After methylphenidate administration it was observed that increased perfusion of the central regions, including the mesencephalon and basal ganglia occurred, which is consistent with activation of dopaminergic neurons in these regions. Experiments on rats showed that methylphenidate increased the local metabolic rate for glucose in mesencephalic, diencephalic and basal ganglia with an accompanying decrease in the motor cortex (Bell, Alexander and Schwartmann, et al, 1982). There was a similar reaction in both the motor cortex and the primary sensory cortex after medication, in the patients observed, suggesting an inhibition of function of these structures, observed clinically as less distractibility and decreased motor activity. The brain stem area has been suggested to be significantly involved in the etiology of Sudden Infant Death Syndrome (Kinney, 1988), pointing, as had been suggested above, to certain similarities with Attention Deficit Hyperactivity Disorder.

In addition, the finding that hypoperfused areas in Attention Deficit Hyperactivity Deficit appear to be located symmetrically in both hemispheres in arterial border zones is consistent with an etiology role for early hypoxic-ischemic lesions (Lou, Hendriksen and Bruhn, 1982). Suggesting once more that there are certain similarities between Sudden Infant Death Syndrome and Attention Deficit Hyperactivity Disorder.

2.2.12 Conclusion

Few children present with pure symptoms of Attention Deficit Hyperactivity Disorder. Most have some other problems. Approximately 40% to 50% of Attention Deficit Hyperactivity Disorder children suffer from learning disabilities of sufficient magnitude that school performance is negatively affected (Lambert, Sandoval, 1980). A similar percentage shows signs of oppositional defiant disorder, a pattern of constantly challenging rules and of resisting disciplinary measures (Rostain, 1991). When the defiance increases to the point where major social rules are broken (eg. lying, stealing, fighting) a diagnosis of conduct disorder is likely. In addition, many children with Attention Deficit Hyperactivity Disorder also exhibit symptoms of internalized problems, including depression, bipolar illness and anxiety. These conditions may exacerbate the child's inattentiveness (Rostain, 1991). Occasionally, a child may present with Tourette's Syndrome, which complicates the clinical picture considerably.

TABLE 2.2

Differential Diagnosis

A. Mental retardation

B. Pervasive developmental disorder (autism)

C. Seizure disorder

D. Disorders of sensory organs, especially deafness

E. Learning disability

F. Other psychiatric disorders

> Adjustment disorders
>
> Conduct disorders
>
> Oppositional disorder
>
> Affective disorders with manic features
>
> Obsessive compulsive disorder
>
> Tourette syndrome
>
> Thought disorders

G. Environmental or family problems

> Inadequate, disorganized, or chaotic environment
>
> Ineffective parenting
>
> Ineffective or inconsistent discipline
>
> Perfectionistic or unrealistic parental expectations lack of "fit" between child's personality and parent's lifestyle or approach to child-rearing
>
> Parental depression or other psychiatric disorders
>
> Marital conflicts
>
> Family stresses, e.g. unemployment, separation, poverty, illness, alcohol or substance abuse

H. Medication-induced attentional problems

I. Age-appropriate overactivity (Rostain, 1991).

As far as the continuum concept is concerned, we may conclude that subclinical damage to the brain does occur and that it may involve psychological sequelae. Rutter (1982) notes that fairly severe damage is needed to give rise to persistent behavioural and cognitive sequelae. Furthermore, such damage does not result in a homogenous, clinical syndrome. Whereas it was previously believed that Attention Deficit Hyperactivity Disorder children outgrew their condition, evidence is mounting that the disorder persists into adolescence and adulthood (Barkley, 1990; Gittleman, 1985; Loney, Kramer Milich, 1981; Mannuzza, Klein, et al., 1988; Satterfield, Hoppe et al, 1982; Satterfield, Satterfield, Schell, 1987; Weiss, Hechtman, et al., 1985). It appears that in excess of 50% of children with Attention Deficit Hyperactivity Disorder continue to exhibit some symptoms of the disorder (eg inattention, impulsivity) into later life. Associated difficulties for adolescents include school failure, aggression, antisocial behaviour, poor social skills, emotional immaturity, low self-esteem and interpersonal conflicts (Rostain, 1991). Adults have an increased incidence of anxiety, low self-esteem, personality disorders, especially antisocial personality disorder, alcohol and substance abuse, interpersonal difficulties and occupational changes. Negative outcomes are associated with factors such as aggression and antisocial behaviour, severity of hyperactivity and impulsivity and the presence of additional individual and family psychopathology, eg alcohol abuse.

The question of how severe this damage must be to result in persistent behavioural and cognitive sequelae is still to be discovered. However, recent studies have definitely involved the frontal lobes, basal ganglia, mesencephalon and brain stem areas, in both Attention Deficit Hyperactivity Disorder, Tourette's Syndrome and Sudden Infant Death Syndrome, suggesting that in these cases the possibility of a neuropsychological organizing principle, and even distinct similarities between these conditions. As Attention Deficit Hyperactivity Disorder and Tourette's Syndrome appears to be broadly speaking, a centrally mediated arousal dysfunction, and Sudden Infant Death Syndrome, again broadly spoken a centrally mediated cardiorespiratory/arousal dysfunction, these areas need to be more closely investigated.

2.3   Gilles de la Tourette's Syndrome

2.3.1   Clinical Features: A Spectrum Disorder

Lang (1992) emphasized the clinical heterogeneity of Tourette's Syndrome which covers a broad spectrum of tic severity as well as behavioural disturbances. A developmental history of hyperactivity has been reported in more than half of Tourette's Syndrome cases (Shapiro & Shapiro, 1978).

77

2.3.2   Definition of Tourette's Syndrome

Tourette's Syndrome is a movement disorder characterised by both motor and vocal (phonic) tics. The generally accepted diagnostic criteria for Tourette's Syndrome are those included in DSM-111-R of the American Psychiatric Association (1987) and are as follows:

- Both multiple and one or more vocal tics, have been present at some time during the illness, although not necessarily concurrently,

- The tics occur many times a day, (usually in bouts) nearly every day, or intermittently throughout a period of more than one year.

- The anatomical location, number, and frequency complexity and severity of the tics change over time.

- Onset is before the age of 21.

- Symptoms do not occur exclusively during psychoactive substance intoxication, or known central nervous system disease, such as Huntington's chorea, and post-viral encephalitis (Robertson, 1989).

However, despite the formulation of these criteria, Tourette's Syndrome is clearly a disorder that is clinically heterogeneous (Robertson, 1988), a problem that has greatly hampered research efforts to identify causal biochemical variables and has led to difficulties in interpreting epidemiologic, genetic, and therapeutic studies. The clinical manifestations of Tourette's Syndrome can best be viewed along a continuum that includes both motor and behavioural features (Robertson 1988).

2.3.3   The Spectrum of the Tic Disorder

Tics are brief, involuntary movements (motor tics) or sounds (phonic or vocal tics) that occur out of a background of normal motor activity. Motor and phonic tics can be divided conceptually into simple and complex forms. Simple motor tics are abrupt, brief, isolated movements, such as an eye-blink, head twitch, shoulder shrug, or facial grimace. Complex motor tics consist of more coordinated and complicated movements that often appear purposeful e.g. smelling, jumping, and hitting. Repetitive sequences of simple motor tics can be considered at the border between simple and complex motor acts. Simple phonic tics include a variety of inarticulate noises and sounds, such as throat clearing, sniffing, and grunting. Complex phonic tics consist of words such as echolalia, papilalia, and coprolalia (Robertson, 1989). The tic disorder of Tourette's Syndrome represents a wide spectrum of involuntary movements and noises, some of which may appear quite bizarre (e.g. throwing objects, pulling down

pants) and can be misinterpreted as manifestations of psychological illness (Fahn, 1982).

Recent attention has focused on sensory symptoms that may occur in Tourette's Syndrome. "Sensory tics" can be defined as patterns of somatic sensations, variously described by patients as feelings of pressure, tickle, warmth, cold, or other abnormal sensation in skin, bones, muscles, and joints (Shapiro & Shapiro et al, 1978). These sensations are localized to specific body regions, such as face, shoulder, or neck, and result in dysphoric feelings. Sensory tics may be the most prominent feature of illness for some patients, are often misdiagnosed, and respond readily to usual tic-suppressing medication (Kurlan, 1989). Chronic multiple tic disorder (motor or phonic) differs from Tourette's Syndrome in that motor or phonic tics, but not both, are present. Recent genetic studies indicate that both Chronic Multiple Tic Disorder and Tourette's Syndrome are transmitted as hereditary traits in the same families, and that Chronic Tic Disorder seems to be a mild form of Tourette's Syndrome (Pauls, Cohen et al, 1988). Transient tic disorder, which differs from Chronic Tic Disorder and Tourette's Syndrome, appears to be a part of the clinical spectrum of Tourette's Syndrome, and a possible expression of the same genetic defect (Kurlan, Behr et al, 1988).

These ideas concerning the relationship between Tourette's Syndrome and Transient Tic Disorder may have far-reaching importance, as 4% - 16% of all children have been reported to have tics at some time in the course of development (Torup, 1972) Although tic severity is known to wax and wane throughout the course of illness, Tourette's Syndrome has long been considered a severe and disabling condition,. However, most cases are mild and do not come to medical attention (Kurlan, 1989).

2.3.4   The Spectrum of Associated Behavioural Disturbance

Although chronic, multiple motor, and phonic tics are usually the most prominent clinical features of Tourette's Syndrome, and represent the signs upon which the diagnosis of the disorder is currently based, tics may also be accompanied by a variety of behavioural disorders. Studies have demonstrated a high incidence of obsessive-compulsive disorder, generally about 50%, in Tourette's Syndrome patients (Pitman, Green, et al, 1987). Pauls et al (1986) studied the rates of Tourette's Syndrome, Chronic Tic Disorder, And Obsessive Compulsive Disorder in 1st-degree relatives of Tourette's Syndrome probands, and found an increased rate of Obsessive Compulsive Disorder in a pattern suggesting that Obsessive Compulsive Disorder may be an alternative expression of the Tourette's Syndrome trait. This theory is supported by segregation analysis of Tourette's Syndrome families which indicates that Obsessive Compulsive Disorder is etiologically related to Tourette's Syndrome and supports autosomal dominant inheritance with sex-specific penetrance and variable expression (Pauls,

79

Leckman et al, 1986). When Obsessive Compulsive Disorder is considered an alternative expression of the putative Tourette's Syndrome gene, penetrance estimates for females rise from 56% (when only Tourette's Syndrome or Chronic Tic Disorder is considered) to 70%.

About 50% of patient with Tourette's Syndrome will show evidence of Attention Deficit Hyperactivity Disorder or Attention Deficit Disorder, manifested by inattention, impulsivity, and hyperactivity (Kurlan, 1988). Pauls et al (1986), found that the rate of Attention Deficit Hyperactivity Disorder among relatives of probands with both Tourette's Syndrome and Attention Deficit Hyperactivity Disorder was 8 times higher than for the probands with Tourette's Syndrome alone, suggesting that the 2 traits segregate independently. Other forms of general behavioural disturbances have been reported to be associated with Tourette's Syndrome. Sleep disturbances in Tourette's Syndrome subjects are common (Van de Wetering, 1988). The abnormalities of sleep which are frequently reported include insomnia, sleep-talking, enuresis, etc. It has been suggested that the sleep disturbances are indicative of a "disorder of arousal". Investigators reported an increase in sleep stages three and four, thus suggesting that Tourette's Syndrome was a disorder of arousal (Glaze et al, 1982). Tourette's Syndrome patients were found to be significantly different from controls for symptoms of inattention, impulsivity, hyperactivity, a variety of conduct disorders and schizoid symptoms.

2.3.5   History

The first clear medical description of Tourette's Syndrome was in made in 1825, when Itard reported the case of a French noblewoman who developed symptoms of Tourette's Syndrome at the age of seven, and who, because of the socially unacceptable nature of her vocalizations, was compelled to live as a recluse until she died (Robertson, 1989). Itard regarded this not as a new disorder, but rather "as one of the most extraordinary forms that clonic convulsions can assume" (Itard, 1825). In 1885, Gilles de la Tourette described nine cases of the same syndrome. In his classic report, De la Tourette gave an account of the onset and progression of symptoms and introduced the term, coprolalia, to describe the use of obscenities (Gilles de la Tourette, 1885). Other cases have been documented since then by various authors. Shapiro et al, (1978) trace the history of Tourette's Syndrome, noting that between 1885 and 1965 only about 50 cases were described in the literature. They divided the history into several periods, with dominating themes including those emphasizing pathogenesis, such as "neuropathic heredity" to predominantly treatment areas, spanning psychoanalysis, behavioural techniques, and chemotherapy.

2.3.6   Prevalence

The exact prevalence of Tourette's Syndrome is unknown. Recent estimates have ranged from 0,03% - 1,6% (Kurlan, Behr, Medved et al, 1987), and have been based on case series of patients referred for treatment, or on data obtained from questionnaires without clinical evaluations (Kurlan, 1991). Systematic analysis of large Tourette's Syndrome kindreds using a family study method in which all available family members are directly interviewed and examined, indicates that most cases of Tourette's Syndrome tics are mild and do not come to medical attention and that the disorder is often unrecognized and misdiagnosed by physicians (Kurlan,1991). Previously reported rates for the prevalence of Tourette's Syndrome are therefore likely to represent gross underestimates. Furthermore, studies of the prevalence of Tourette's Syndrome have been restricted to an analysis of the tic disorder, and mounting evidence indicates that behavioural disorders, including Obsessive Compulsive Disorder and Attention Deficit Hyperactivity Disorder, may be the only clinical manifestations of illness for some individuals. Therefore, the prevalence of the disorder may be much higher than current estimates, especially if behavioural manifestations are included (Cohen,1988).

In conclusion, the exact prevalence of Tourette's Syndrome is unknown, and currently accepted figures are almost certainly underestimates.

2.3.7   Epidemiology

Tourette's Syndrome is found in all cultures and racial groups, but is rare among the American black population, which has been represented in varying, but small proportions in a number of studies: 0,5% (Shapiro et al, 1973), 1,8% (Comings & Comings, 1985), and 8,7% (Golden, 1984). Most case reports have come from the U.S.A. (Kidd et al, 1980; Nee et al, 1980; Golden, 1984) and a significant number of patients have also been reported from the U.S.S.R. (Pushkov, 1986). However, the disorder has a worldwide distribution. Some studies have found an unexpectedly large proportion of their Tourette's Syndrome subjects have an East European/Ashkenazim-Jewish background (Eldridge et al, 1977; Shapiro et al, 1978). However, these studies were from Metropolitan New York which has a large Jewish population, possibly explaining the bias (Robertson,1989).

2.3.8   Demography

Most studies and reviews agree that Tourette's Syndrome appears three to four times more commonly in males than in females (Kelman, 1965; Shapiro et al, 1978; Golden, 1984; Van de Wetering et al,

81

1989). The syndrome is found in all social classes (Shapiro et al, 1989; Nee et al, 1980). Robertson et al (1988) reported that a significant percentage of their patients failed to attain their parental social class. This suggests that patients with Tourette's Syndrome may well underachieve socially. Shapiro & Shapiro (1982a) state that there is no evidence that any of the demographic or illness-related variables significantly distinguish patients with Tourette's Syndrome from normal controls: parents; age at time of patient's birth, birth order, birth weight, history of abortions, perinatal complications, patient's medical history, or family medical history. Other authors reported possible birth complications in 25% (Lees et al, 1984) and 40% (Lucas et al, 1982) of their sample.

2.3.9   Psychopathology

The psychopathology of Tourette's Syndrome subsequent to 1965 is rather controversial, Shapiro & Shapiro, (1982a) have not noted an association between Tourette's Syndrome and any specific psychiatric syndrome or psychodynamic factors. However, in a recent study, only one patient in 34 was free from psychiatric illness, the majority being diagnosed as having various types of personality disorders (Shapiro et al, 1978). They maintain that there may be a subgroup of Tourette's Syndrome patients, who experience difficulty with compulsive ritualistic behaviour, but there did not appear to be any defining characteristics of this subgroup. Corbett et al (1969) studied the psychopathology of tigueurs, including patients with Tourette's Syndrome, with that of disturbed children, and found that tigueurs had significantly more habit disorders, obsessional symptoms and hypochondrias, and fewer conduct disorders. Phobic features were common. Robertson et al (1988) noted significantly more depression in patients than in controls. Depression correlated with early onset and longer duration of the disorder, while coprolalia was associated with increased hostility scores. Significant associations emerged between psychopathological variables and neurological or electroencephalogram (EEG) abnormalities.

Finally, it does appear that patients with Tourette's Syndrome are especially prone to depression, which is probably related to the duration of the syndrome. This could be caused by the fact that the sufferers have a chronic, socially disabling stigmatizing disease. A genetic predisposition to depressive illness should also, however, be borne in mind.

(1)   Obsessional Disorder

Previous studies have suggested that Obsessive Compulsive symptoms frequently occur among patients with Tourette's Syndrome. Paul et al, (1986) found the rate of Obsessive Compulsive Disorder among

82

1st degree relatives was significantly increased over estimates from the general population and a control sample of adoptive relatives. The rates of Tourette's Syndrome, Obsessive Compulsive Disorder and Chronic Motor Tics were virtually the same in families of probands with Obsessive Compulsive Disorder when compared with families of probands without Obsessive Compulsive Disorder. The frequency of Obsessive Compulsive Disorder without Tourette's Syndrome or Chronic Motor Tic among 1st degree relatives was significantly elevated in families with both Tourette's Syndrome, Obsessive Compulsive Disorder and Tourette's Syndrome-Obsessive Compulsive Disorder probands, suggesting that the same forms of Obsessive Compulsive Disorder may represent an alternative expression of the factors responsible for Tourette's Syndrome and/or Chronic Motor Tic Disorder.

It has been suggested that the development of Obsessive Compulsive Disorder symptoms is part of the natural course of illness of patients with Tourette's Syndrome. Pauls et al (1986) suggests that there may be more than one association between Obsessive Compulsive Disorder and Tourette's Syndrome. Since some of the 1st degree relatives who had Obsessive Compulsive Disorder never experienced motor or phonic tics, their results suggest that in families of patients with Tourette's Syndrome, members may express obsessional symptoms without first developing Tourette's Syndrome or Chronic Motor Tics. This may represent a different clustering of behaviours in the spectrum of symptoms associated with this syndrome. It has been suggested that Tourette's Syndrome and Obsessive Compulsive Disorder are etiologically related, at least within biologic families or patients with Tourette's Syndrome, and that Obsessive Compulsive Disorder represents a different manifestation of the same underlying factors responsible for the expression of Tourette's Syndrome and Chronic Motor Tics. Green And Pitman (1986) conducted a similar study comparing patients with Tourette's Syndrome to those with Obsessive Compulsive Disorder and a normal control population. Of the 16 patients with Tourette's Syndrome, four of the nine males and six of seven females met DSM 111 criteria for Obsessive Compulsive Disorder (disregarding the DSM 111 exclusion of the Obsessive Compulsive Disorder diagnosis in the presence of Tourette's Syndrome). Interestingly, the Obsessive Compulsive Disorder cohort also showed a similar pattern of symptom overlap, in that 69% had either a personal or family history of tics, in comparison with only 6% of the controls.

The precise phenomenology of obsessional thoughts and behaviour have been widely reported, except that arthmomania (counting rituals or obsessions with numbers) and "evening up" or a concern with symmetry, checking and arranging, are common. This is of particular importance, as despite the fact that a relationship between obsessive compulsive phenomenon in Tourette's Syndrome and coprolalia has been reported, (Robertson et al, 1988) the thought and rituals were generally not dominated by diet, germs and fear of contamination. Cummings and Frankel (1985) comment on similarities between

83

Tourette's Syndrome and Obsessive Compulsive Disorder, including age of onset, lifelong course, waxing and waning of symptoms, involuntary, intrusive, ego-alien behaviour and experiences, occurrences in the same families, and worsening with depression and anxiety. The debate for a clear association between Tourette's Syndrome and obsessional disorder also comes from the recent findings of Kurlan et al (1986), Pauls et al (1986a,b) and Comings and Comings (1987b), who found that many relatives of Tourette's Syndrome patients describe obsessive compulsive thoughts and actions in the absence of tics or vocalizations, which, they believe, suggests that Tourette's Syndrome and Obsessive Compulsive Disorder may be etiologically related.

Therefore, apparently obsessional disorder is an integral part of Tourette's Syndrome, and in this context, it is of interest to note that Pierre Janet, 1903, described three clinical stages of psychasthenic illness; the first was the "psychasthenic state", the second, "forced agitations", which include motor tics, while the third was obsessions and compulsions (Pitman, 1987). Robertson (1989) speculates that there is a genetic basis to Tourette's Syndrome and that the phenotype may be expressed on a spectrum, with Tourette's Syndrome alone at one end, Tourette's Syndrome and a variety of tic disorders (with or without obsessional disorders in the middle, and more obsessional disorder at the other end. It is further suggested that the type of obsessional disorder found on this spectrum is possibly different from that in the majority of DSM 111-R obsessional disorder subjects.

(2)   Family Psychopathology

If psychopathology is an integral and distinctive feature of Tourette's Syndrome, a positive family history of psychiatric illness is to be expected. Montgomery et al (1982) found that 70% of 30 1st degree relatives of 15 Tourette's Syndrome patients satisfied Feighner criteria for psychiatric illness, the most common diagnosis being unipolar depression, obsessive compulsive illness, and panic disorder. More recently, Green and Pitman (1986) and Pauls et al (1986a & b) found the incidence of Obsessive Compulsive Disorder significantly higher among Tourette's Syndrome relatives than control populations. A significant proportion, 49%, of probands had a positive family history of psychiatric illness, of which the most common disorders were depression, schizophrenia, and obsessional disorder (Robertson et al,1988). It would thus appear that there is a rise in psychiatric morbidity in the relatives of Tourette's Syndrome patients, with special emphasis on obsessional disorder and possibly depression.

2.3.10   Etiology and Pathogenesis

Recent biochemical research has largely focused on efforts to identify etiological factors and

84

pathophysiological mechanisms active in Tourette's Syndrome and to develop safe and effective psychopharmacological interventions (Leckman, Walkup, Riddle, 1987). In addition to the motor tics and vocal noises, it is associated with a wide range of other features, including Attention Deficit Hyperactivity Disorder, Learning Disabilities, stuttering and other speech problems, coprolalia, echolalia, discipline problems, Conduct Disorder, Obsessive Compulsive Disorder, and others (Eldridge et al, 1977; Golden, 1978; Shapiro et al, 1978; Nee et al, 1989; Fredhoff & Chase, 1982; Cohen et al, 1983).

Although in his early writings, Gilles de la Tourette considered the disorder to be hereditary, for many years the etiology of Tourette's Syndrome was ascribed to psychogenic causes and the importance of genetic factors was neglected. There is evidence of familial transmission (Kurlan et al, 1987; Nee, Caine et al, 1980; Pauls and Leckman, 1986; Vieregge, Shafer et al, 1988).

Some speculate that a single gene is responsible for Tourette's Syndrome symptoms (Comings, 1987). No gene or suspected chromosome has yet been identified, and controversy continues among geneticists about how a single gene could be responsible for a panoply of behavioural manifestations from attention deficits to compulsive eating problems (Merz, 1989). Unfortunately, many Tourette's Syndrome criteria have proven to be inaccurate, which has necessitated repeated changes to the diagnostic criteria. Attention Deficit Hyperactivity Disorder has suffered the same problems and was initially known as Minimal Brain Dysfunction. Tourette's Syndrome is a diagnostic label for a disorder of presumably unknown etiology, that is lacking in biochemical or neurologic confirmation, and relies solely on observable, yet changing criteria (Gedye, 1991). Recently, there has been an unexplained increase in the number of dual-diagnosis cases, Tourette's Syndrome has been reported to co-occur with another disorder, either with a known etiology such as Down's Syndrome, or with an unknown etiology, such as Attention Deficit Hyperactivity Disorder, hyperactivity, mental retardation due to unknown cause, Obsessive Compulsive Disorder, and psychosis (Comings, 1987b). Cohen et al (1982) state that Tourette's Syndrome reflects the interaction among genetic neuropsychological, behavioural, and environmental factors.

In the late 70's investigators demonstrated that Tourette's Syndrome and chronic tics show a familial concentration, and in families with Tourette's Syndrome, Chronic Motor Tics appears to represent a milder form of the same illness (Pauls,, Cohen et al, 1988). Susceptibility to both Tourette's Syndrome and Chronic Motor Tics is transmitted vertically from generation to generation, indicating a genetic influence (Price, Kidd, et al, 1986). Single-major-locus, polygenic, and multifactorial patterns of transmission within families have been proposed. However, the most widely held idea of transmission

pattern derives from segregation analysis of 30 families affected by Tourette's Syndrome which indicates that the disorder is inherited in an autosomal dominant pattern with incomplete and sex-specific penetrances (affected males are more common than affected females) and variable expression, including Tourette's Syndrome Chronic Motor Tics, and Obsessive Compulsive Disorder (Pauls and Leckman, 1986). It is now generally accepted that the most cases of Tourette's Syndrome are genetically determined (Kurlan, 1989). The recognition of a specific inheritance pattern for Tourette's Syndrome and the identification of large kindreds affected by the illness, have raised hopes that the application of pedigree analysis, using modern recombinant DNA technology, be able to identify a genetic marker linked to the disease (Kurlan, Behr, et al, 1989).

In conclusion, there is consensus of opinion that Tourette's Syndrome is probably inherited by an autosomal single dominant gene with varying penetrance. There are some suggestions that the same gene can be expressed as an obsessive compulsive disorder. There is no conclusive proof, as yet, that the gene may be expressed as Attention Deficit Hyperactivity Disorder (Kurlan et al, 1986).

Eldridge and Denkla (1987) suggest that a complex interaction of androgenic and immunological factors are involved in susceptibility to neurodevelopmental disability, and therefore, Tourette's Syndrome. Bonnet (1982) tackled the anatomical localization of Tourette's Syndrome by focusing on neurochemistry and the anatomical substrates of vocalizations and various movements, such as blinking and tics. He concluded by suggesting that the biochemical structures of the limbic forebrain structures, particularly the anterior cingulate cortex and their interrelationships with the specific nuclei of the tegmentum, renders the cingulum the possible site for Tourette's Syndrome.

(1)   Frontal Lobe Dysfunction

Gedye (1991) has postulated an interesting hypothesis in which frontal lobe dysfunction is indicated. The conclusion reached is particularly appealing because it accounts for the vagaries in diagnostic criteria, the dual diagnosis, and the difficulty in finding biochemical correlates for all cases. Gedye (1991) makes the following premises:

1.   Tourette's Syndrome tics/movements are involuntary

2a.   Tourette's Syndrome tics result from abnormal discharges in the frontal lobe(s) that cause innervation of numerous muscles.

2b.   Duration and recurring nature of Tourette's Syndrome movements are similar to duration and recurring nature of involuntary movements during frontal lobe seizures.   ·   -

2c.   Neurologic studies report frontal lobe involvement in Tourette's Syndrome.

3.   Numerous etiologies can result in frontal lobe epilepsy.

4.   Etiologies known to cause frontal lobe seizures are reported as co-occurring with Tourette's Syndrome.

Based on these premises, he concludes that abnormal discharges in the frontal lobe(s) particularly the motor area in the mesial basal region, are the final common dysfunction that causes diverse phenomena, labelled as Tourette's Syndrome.

To have a common site of dysfunction is not an etiology per se. Numerous etiologies can result in frontal lobe seizures (Quesney, Kruger et al, 1984; Rasmussen, 1975). Obviously,different etiologies produce differences in the extent (localized trauma); type (neurochemical imbalance); and location (orbital frontal, medial frontal) of damage. As there is such variation in extent and type of damage, it is feasible that some cases might benefit from one medication, while others do not (Mesulam & Petersen, 1987; Nee et al, 1980). Some Tourette's Syndrome cases show disturbance in many frontal cortical functions eg difficulty attending, planning, sequencing, changing set, go-no-go tasks, obsessive-compulsiveness, and impulsivity, which implies extensive damage; others do not. Comings and Comings (1987a) have suggested that some problems shown by Tourette's Syndrome cases such as appetite and sleep disturbances, suggest limbic involvement. The wide variety of etiologies that cause frontal lobe seizures account more readily for the heterogeneity in clinical presentation of Tourette's Syndrome than can a single-gene theory (Gedye, 1991).

Numerous neurologic studies on frontal lobe seizures provide specific examples of involuntary facial, vocal, and limb movements that are caused by dysfunction in the frontal lobes. Neural disturbance in the "motor" strip is often localized in the mesial/mesiobasal area of the brain (Gedye,1991). As there are several hundred muscles in the human body, it is understandable how disparate the motor manifestations can be from one patient to the next, or even in the same patient, from one time to the next (Shapiro et al, 1978). Abnormal discharges in the frontal lobes are known to cause vagul nerve stimulation that manifests as respiration and blood pressure changes (Buchanan, Valentine & Powell, 1985: Hurley-Guis & Neafsey, 1986). Thus, various breathing changes, plus the possible permutations of 56 vocal muscles can result in gasps, grunts, barks etc.

Direct evidence of frontal lobe involvement in Tourette's Syndrome patients comes from brain scan studies. Chase et al, (1984) noted that position emission tomography (PET) scans in Tourette's Syndrome adults showed that the more severe the tics, the lower the glucose metabolism, mainly "in

87

the middle and inferior portions of the frontal lobes bilaterally". Devinsky (1983) proposed that the "periaqueductal gray and midbrain tegmentum may be involved in Tourette's Syndrome". Comings (1987) has supported the idea that the ventral tegmental area is a primary site of pathology in Tourette's Syndrome, related to an imbalance in the mesencephalic-mesolimbic area. Neuropsychological testing of Tourette's Syndrome patients has revealed "abnormalities in the right temporal and orbital cortical functions" (Sutherland, Kolb, School et al, 1982). Other neurological evidence connects Tourette's Syndrome symptoms to frontal lobe functioning.

Conjugate head and eye movements arise from stimulation to frontal cortical fields (Delgado et al, 1982; Kluin, Abou-Khalil, & Hood, 1988: Waterman et al, 1987). Hyperactivity, which often co-occurs with Tourette's Syndrome (Pauls et al, 1986; Sandyk & Bamford, 1988: Sverd, Curley, Jandorf et al, 1988), has been connected to disturbed frontal lobe functioning (Chelune, Ferguson, et al, 1986; Gerbner, 1973; Lou, Henrikson et al, 1987; Mattes, 1980; Pauls et al, 1986; Stuss & Benson, 1983). This is also the case with impulsiveness (Luria, 1973). Attention deficits, which often co-occur with Tourette's Syndrome (Cohen et al, 1979; Comings & Comings, 1987a; Goldman, 1988; Leckman et al, 1986; Matthews, 1988; Pauls et al, 1986) have been ascribed to frontal lobe disturbances (Luria, 1973; Mesulam,1986; Stuss & Benson, 1983).

Circumstantial evidence links Tourette's Syndrome to neurotransmitter imbalances and neurotransmitter receptors in the frontal lobes. Various researchers have implicated disturbances in both dopamine and serotonin levels in Tourette's Syndrome (Bunney & DeReimer, 1982; Lakke & Wilmink, 1985; Matthews, 1981; Singer, Pepple et al, 1978). Some neurologists speculated that in Tourette's Syndrome an "imbalance exists between central dopamine and serotonin" (Singer et al, 1978). It is of interest that the highest concentration of dopamine receptors in the brain is in the medial-prefrontal area and cingulate cortex (Brown, Crane et al, 1979; Emson & Kolb, 1978), an area in which frontal lobe seizures often originate (Waterman et al, 1987). Gedye's (1991) hypothesis states that non-genetic forms of frontal lobe dysfunction present as sporadic forms of Tourette's Syndrome, and that inherited ones present as familial forms of Tourette's Syndrome. A single gene defect could still be a valid explanation when manifestations of frontal lobe dysfunction occur in other members of the family (Gedye, 1991). Numerous etiologies known to cause frontal lobe seizures have been reported in children diagnosed with Tourette's Syndrome. Co-occurring disturbances, such as obsessive- compulsiveness, and attention deficits have been traced to frontal lobe dysfunction.

2.3.11 Sleep Disorders

Tourette's Syndrome is a neurologic disorder, beginning in childhood, characterised by multiple motor and vocal tics in a chronic, but fluctuating course. Afflicted patients frequently report difficulty with falling asleep, or staying asleep, and excessive restlessness during sleep (Nee, Caine et al, 1980; Mendelson, Caine et al, 1980). In a study on 14 patients with Tourette's Syndrome carried out by Glaze et al, (1983), overnight polygraphic sleep studies, which included accelerometry and video monitoring, were used. In 11 of 12 Tourette's Syndrome patients, tic-like movements, similar to those observed during wakefulness, and rare vocalizations, occurred during all stages of sleep. 7 of 12 Tourette's Syndrome patients had unusual behavioural episodes. These occurred during stage 4 sleep and were characterised by a sudden and intense arousal, apparent disorientation, confusion, or combativeness, or both, increase in tic activity, and occasional automatism-like activities. During these episodes, the EEG changed from a stage 4 sleep pattern to generalized, high-voltage, monomorphic, rhythmic delta activity, lasting 10 -20 seconds and followed by a return to the normal sleep or awake EEG pattern. They occurred 2 to 5 times during the night and were not associated with any cardiac arrhythmias or changes in respiratory pattern; they were not observed in control subjects. Waking EEG's in 11 of 14 Tourette's Syndrome patients and in all control subjects were normal (Glaze, Frost et al, 1983).

Three patients had frequent apneic episodes. Apneic spells were found amongst siblings of Sudden Infant Death Syndrome infants. It thus appears that these subgroups have apneic episodes in common. Although it has often been maintained that tics, like other involuntary movements disappear during sleep, this study demonstrates that they may persist. Furthermore, it also shows that Tourette's Syndrome patients have disturbed sleep patterns. 6 of 14 patients gave a history of sleep disturbances, including enuresis, somnambulism, and frequent awakenings. A similar high percentage of parasomnias in Tourette's Syndrome patients have been reported by other researchers (Nee, Caine et al, 1980; Hashimoto, Edno et al, 1981; Moldofsky, Tullis et al, 1974). Nee et al (1980) reported that 16 of 32 patients with family histories of Tourette's Syndrome or tics and only 5 of 18 with negative family histories had sleep disturbances. These results suggest that sleep disturbances are significantly increased in Tourette's Syndrome patients with a positive family history of Tourette's Syndrome or tics. The occurrence of sleep disturbances, in addition to age of onset, presence of abnormalities on the neurologic examination, ethnic composition, (Golden, 1978), and response to haloperidol (Nee et al, 1980), appears to differentiate familial from non-familial Tourette's Syndrome patients (Glaze, Frost et al, 1983).

The recorded sleep pattern of untreated Tourette's Syndrome patients was characterised by increased

amounts of stage 3/4 slow wave sleep, decreased rapid-eye-movement sleep, and increased numbers of awakenings and tics. Furthermore, these Tourette's Syndrome patients frequently experienced paroxysmal episodes during stage 4 slow-wave sleep that were similar to night terrors. Broughton (1968) has suggested that night terrors are essentially disorders of arousal. Glaze et al, (1983) suggest that the disturbed sleep patterns in these Tourette's Syndrome patients may be secondary to a disorder of arousal. In infants and young children, arousal is associated with an EEG pattern of high-voltage, rhythmic, delta waves (Kellaway, 1979). This immature arousal pattern may persist in Tourette's Syndrome patients, as, in the adolescent and young adult patients in the study who had stage 4 paroxysmal events, the EEG initially was characterised by the high-voltage, rhythmic, generalised, very slow activity (Glaze, Frost et al, 1983).

An involvement of dopaminergic mechanisms in Tourette's Syndrome is supported by improvement with haloperidol, a dopamine-blocking medication, and by exacerbation with drugs that promote dopaminergic hyperactivity (dextroamphetamine and methylphenidate) (Bruun, Shapiro, et al, 1976; Golden, 1974; Lowe, Cohen et al,1982). Reviews of electrophysiologic, pharmacologic, and biochemical studies concerning the role of the central monoamine containing neurons in the induction and maintenance of various stages of the sleep-wakefulness cycle, have indicated the importance of serotonin pathways for the maintenance of slow-wave sleep and for the induction of paradoxical or rapid-eye-movement sleep and catecholamine pathways for the maintenance of wakefulness and rapid-eye-movement sleep (Fux, Lidbrink, 1973). Ascending central dopamine pathways appear important for behavioural arousal (Fux, Lidbrink, 1973; Mornier, Galliard, 1980). An imbalance in the systems may underlie the findings in the study by Glaze et al, 1983).

The brief apneic episodes experienced by some Tourette's Syndrome patients may be associated to the role of arousal mechanisms in obstructive apnea suggested by Sullivan and Issa (1980). It was concluded by the above, that the arousal response is the critical factor in relief of obstructive sleep apnea. Elements that raise the arousal threshold include sleep fragmentation (Bowes, Woolf et al, 1980), and chronic recurrent hypoxemia, which may cause depression of neurotransmitter synthesis (Sullivan & Issa, 1980). Children diagnosed as suffering from Attention Deficit Hyperactivity Disorder frequently manifest the inability to fixate attention for long periods, forgetfulness, and increased distractibility. The manifestation of these cognitive problems in direct relation to increased activation strongly suggests that in Attention Deficit Hyperactivity Disorder children, the attentional problems may be the result of a poorly modulated level of activation (Wender, 1971).

A significant proportion of Sudden Infant Death Syndrome siblings manifested similar increased

modulation. Another aspect of poor modulation of activity, is the tendency of some Attention Deficit Hyperactivity Disorder children to sleep either restlessly, or particularly heavily. This is of interest because of the significant percentage of enuresis found in Attention Deficit Hyperactivity Disorder children (Rie & Rie, 1981). Studies of sleep patterns in enuretics, many of whom are presumably Attention Deficit Hyperactivity Disorder sufferers, have shown that they may have "disorders of arousal". Enuretics are difficult to arouse from non-dreaming sleep and yet show excessive levels of activation throughout sleep (Wender, 1971). Harper, Leake et al 91981) demonstrated, in a series of studies, that subsequent siblings of Sudden Infant Death Syndrome victims have decreased spontaneous arousals during sleep.

It is suggested by two pieces of evidence that the excessive activity is a release phenomenon, a manifestation of a hypo-active inhibitory system;

-       The appearance of the syndromes following destructive lesions of the central nervous system
        eg. hypoxia, encephalitis, and,

-       the response of the syndromes to stimulant drugs (Wender, 1971).

Harper, Hoppenbrouwers et al (1978) undertook a series of studies in which they demonstrated that subsequent siblings of Sudden Infant Death Syndrome victims have decreased voluntary arousals from sleep. Additional studies by Ward and Associates (1986), of siblings of Sudden Infant Death Syndrome victims found that they arouse only 27% of the time when challenged with breathing 11% inspired oxygen during sleep. It therefore appears that siblings of Sudden Infant Death Syndrome victims exhibit a disorder of arousal, as manifested by the other three subgroups, namely Attention Deficit Hyperactivity Disorder, Attention Deficit Disorder, and Tourette's Syndrome. It is therefore possible that Sudden Infant Death Syndrome not only shows significant overlap with Attention Deficit Hyperactivity Disorder, Attention Deficit Disorder, and Tourette;s Syndrome, but that it could, with the other disorders mentioned, share a broadly defined generalized neuropsychological risk factor.

2.3.12   Electrophysiological Studies

Recent clinical and biochemical investigations support an organic cause for Tourette's Syndrome (Butler, Koslow et al, 1979; Cohen, Shaywitz et al, 1979; Kidd, Prusoff et al, 1980; O'Quinn, Thompson, 1980; Shapiro, Shapiro et al, 1973). Electroencephalographic (EEG) abnormalities are reported in over 50% of patients and in some studies imply an epileptic basis for the disorder (Krumholz, Singer et al,

1983). Evoked response abnormalities to visual stimuli, which are described in other involuntary movement disorders have been reported in patient with Tourette's Syndrome (Domino, Piggott et al, 1982). Furthermore, specialized recording techniques have demonstrated an absence of slow premotor potential preceding tics in Tourette's Syndrome (Obeso, Rothwell et al, 1981). Krumholz et al 91982) noted that the majority of EEG abnormalities in their research were classified as mild; slight excess of background slowing or slowing of the normal alpha rhythm. The major difference between the patients with Tourette's Syndrome and control subjects was in the amplitude of the visual evoked response which was lower in the affected patients. EEG abnormalities in most of the patients consisted of excessively slow activity. Bergen et al (1981) question the significance of the EEG in reflecting the pathophysiological basis of the disorder, as there is a lack of a consistent type of abnormality and suggest that some of the findings are related to additional heterogeneous central nervous system lesions in some patients. The few autopsy studies available do not implicate the cerebral cortex (Shapiro, Shapiro et al, 1972), and the normal intellectual function of most patients with the disorder confirms sparing of cortical systems (Shapiro, Shapiro et al, 1978). Therefore, it is not surprising that EEG rhythms, which probably reflect cortical and thalamo-cortical activity do not show a characteristic disturbance in patients with the disorder (Anderson, Anderson et al, 1976; Creutzfeldt, Houchin, 1976). Tourette's Syndrome appears similar to other movement disorders eg. tardive dyskinesia, which are suspected to result from dysfunction of central dopaminergic pathways and which typically produce no characteristic EEG disturbances (Kiloh, McComas, Osselton, 1972).

2.3.13   Associated Features

Robertson (1989) believes that some types of behaviour such as obsessive-compulsive disorder are intimately linked to Tourette's Syndrome and are probably an integral part of the syndrome. Other disturbances, such as hyperactivity, attention deficit disorder, and learning disability occur in a substantial proportion of patients. Aggressive behaviour has been reported in patients with Tourette's Syndrome (Moldofsky et al, 1974; Stefl, 1984). Comings and Comings (1985) noted that discipline problems occur in 41% of females and 45% of males, being one of the main recurrent themes. It is generally accepted that many children who progress to Tourette's Syndrome, first manifest various behavioural disturbances, often labelled minimal brain dysfunction, hyperactivity, or attention deficit disorder (Shapiro et al, 1973) It is of note that the behavioural symptoms of Tourette's Syndrome are subject to the same waxing and waning as the motor and vocal symptoms, or can even persist after the characteristic tics and sounds have largely disappeared (Lechman & Cohen, 1983). Comings and Comings (1987a) found that Tourette's Syndrome patients were significantly different from controls for symptoms of inattention, impulsivity, hyperactivity, a variety of conduct disorders (aggression, fighting

etc.) and schizoid symptoms (thinking that people were plotting against them). However, it must be noted that the majority of Comings and Comings findings and suggestions are not in accordance with the current literature on Tourette's Syndrome or the opinions of several specialists in the field, and his findings seriously questioned (Pauls et al, 1988).

2.3.14   Neuropsychology

Several investigations noted significant discrepancies between verbal and performance scores. Language skills appear to be largely unimpaired, while deficits in visuopractic performance have been documented by a number of authors (Golden, 1984). Shapiro et al (1978) found subtle neurologic deficits in a group of patients. 20% were left-handed or ambidextrous. Most, 78% had minor motor asymmetry, while 20% had chorea or choreoathetoid movements, Other abnormalities included poor coordination, reflex asymmetry, and nystagmus. Cohen et al (1982) stated that Tourette's Syndrome reflects the interaction between genetic, neurophysiological, behavioural, and environmental factors. Eldridge and Denkla (1987) suggest that a complex interaction of androgenic and immunological factors are involved in susceptibility to neurodevelopmental disability and therefore Tourette's Syndrome. They note that, when viewed in this context, the opinion of Balthasar (1957) of an increased number of neurons in the caudate and putamen, suggesting the persistence of an immature neuronal pattern, may be more acceptable (Eldridge & Denkla, 1987).

Golden (1984) identified examples of organic factors including "encephalopathy" on the Bender Gestalt test, a performance discrepancy of more than 15 points and evidence of dysfunction on the Halstead Reitan-Indiana Neuropsychological Assessment Battery. Impairments in coding, written arithmetic, and copying tasks constitute a relevant and interesting cluster. The communality of function among these various tasks is considered to represent a dysfunction of non-constructional visuopractic abilities (Incagnoli & Kane, 1981). Several researchers (Sweet, Bruun et al, 1974; Sweet, Solomon et al, 1973) consider the etiology of Tourette's Syndrome to involve a neurophysiological disorder of the central nervous system, probably the basal ganglia. The role of the basal ganglia in regulating motor function is widely known. Pribram (1977) has stressed the importance of the basal ganglia for sensory input in primates, especially in relationship to visual processing. While the deficits are typically considered cortical in nature, it is not known whether these impairments are secondary results of neurophysiological irregularity of the basal ganglia, or whether they are manifestations of a primary lesion of the cerebral cortex (Incagnoli & Kane, 1981).

Bornstein et al (1983) studies confirmed the findings of previous studies. They suggest that the deficits

found might implicate the right cerebral hemisphere. The presence of bilateral visuomotor and sensory perceptual deficits would not be completely incompatible with this, as previous research has suggested that bilateral tactile perceptual deficits are found after right hemisphere lesions, whereas only contralateral deficits are associated with left hemisphere lesions (Boll, 1974). If the underlying abnormality in Tourette's Syndrome is neurochemical, it may be that the right hemisphere is somewhat more susceptible to disruption than the left hemisphere. It has been suggested that the hemispheres have different patterns of neural organization in that the right hemisphere is more diffusely organized (Gur, Packer, et al, 1980). This more diffuse organization might increase the vulnerability of the right hemisphere to a neurochemical abnormality. The variability among subjects which has been observed in neurological studies of Tourette's Syndrome patients argues against a specific or focal lesion as the source of neuropsychological deficits (Bornstein et al, 1983). It is suggested that the data point to a diffuse subcortical disturbance, probably neurochemical, which produces behavioural deficits which appear to implicate the right cerebral hemisphere more than the left.

2.3.15 Neuroanatomy

Alterations in the dopaminergic system are well documented in Tourette's Syndrome. Dopamine receptor blockers often relieve symptoms, whereas dopamine agonists acutely exacerbate them (Devinsky, 1983). The cluster of symptoms, and known localization of lesions in encephalitis lethargica together with studies on the anatomy of vocalization, suggest that damage to the periaqueductal grew and midbrain tegmentum may be involved in Tourette's Syndrome. Alterations in several neurotransmitter systems have been demonstrated in unmedicated patient with Tourette's Syndrome, the most consistent changes are seen in the dopaminergic and serotonergic systems. Furthermore, there are patients in whom motor and vocal tics develop when neuroleptic therapy is discontinued. These observations are consistent with the hypothesis that tics are caused by stimulation of supersensitive dopamine receptors. With the exception of a small hypothalamic pathway, all central dopamine is produced in the midbrain (Devinsky, 1983). Circuitry sufficient to produce a varied group of affective vocalizations exists in the midbrain and lower brainstem. Although limbic, hypothalamic, and extrapyramidal structures are involved in emotional vocalization, the mesencephalic central gray and tegmentum appear to play a major role. The role of the midbrain in the pathophysiologic mechanism of Tourette's Syndrome remains speculative (Devinsky, 1983). The application of modern techniques-including electron microscopy, tests for the presence of foreign antigens, or abnormal genetic material and assays for neurotransmitters, enzymes, and receptors may provide new insights into the etiology of Tourette's Syndrome.

2.3.16   Conclusion

The above review of Sudden Infant Death Syndrome, Attention Deficit Hyperactivity Disorder, Attention Deficit Disorder , and Tourette's Syndrome contain many common symptoms and similarities. All the above appear to have frontal lobe involvement, abnormal EEG patterns, disorders of arousal, and perinatal risk. Neurodevelopmental "soft" signs and minor physical anomalies are found in both Sudden Infant Death Syndrome siblings and children diagnosed as Attention Deficit Hyperactivity Disorder and Attention Deficit Disorder sufferers. However, no literature could be found on the presence of "soft" signs or minor physical anomalies in Tourette's Syndrome patients. However, it is reasonable to assume that, as Tourette's Syndrome patients often manifest symptoms of Attention Deficit Hyperactivity Disorder, "soft" signs, and minor physical anomalies would be found. The male to female ratio is also similar, as males have an increased risk for the disorders reviewed. Tourette's Syndrome often manifests with other behavioural disorders such as Attention Deficit Hyperactivity Disorder. Frequently, Tourette's Syndrome patients first manifest with Attention Deficit Hyperactivity Disorder, and later develop vocal or motor tics. It thus appears that Tourette's Syndrome patients will show evidence of Attention Deficit Hyperactivity Disorder, manifested by inattention, impulsivity, and hyperactivity.

Furthermore, there is strong evidence that these neuropsychological disorders reviewed are genetically determined. An important confounding factor in the determinations of prevalence and nature of inheritance is the fact that the complete range of acceptable manifestations of the disorders have not been fully established. It is believed that the gene responsible for Tourette's Syndrome can be manifested as Tourette's Syndrome alone, chronic multiple tic disorder,(usually motor but rarely phonic) and/or obsessive-compulsive disorder. Kurlan et al (1989) have presented evidence that transient tic disorder may also be a manifestation of the gene. The possible genetic relationship between Tourette's Syndrome and Attention Deficit Hyperactivity Disorder is currently controversial. Despite the common association between the two disorders, with approximately 50-60% of studied Tourette's Syndrome patients demonstrating some features of Attention Deficit Hyperactivity Disorder, many authors believe that Attention Deficit Hyperactivity Disorder and Tourette's Syndrome segregate independently and that these are comorbid conditions rather than genetically linked.

Comings (1987) suggests "semi-dominant - semirecessive" inheritance; the more severe cases inherit the disorder in a homozygous fashion while those manifesting only the behavioural disorders represent a heterozygote state (presented at Boston Symposia, 1991). This hypothesis is quite contrary to the mainstream opinion which supports a sex-influenced, autosomal dominant mode of inheritance with

variable expressivity as either Tourette's Syndrome, Chronic Motor Tic Disorder or Obsessive Compulsive Disorder. Assessing Tourette's syndrome families, it is evident that the apparent penetrance depends on the sex of the offspring and the nature of the accepted phenotype (Lang, 1992).

Several studies have provided evidence that Attention Deficit Disorder may be transmitted within families. Twin and adoption studies suggest that this familia clustering may be due to genetic factors. Preliminary studies by Pauls et al (1992) support the hypothesis that there is a strong familial clustering for Attention Deficit Disorder. The observed patterns suggest that vertical transmission of the disorder occurs and that the sex difference observed in the population prevalence might be explained in a threshold effect. Logistic analyses indicate that a model that includes sex of the proband, parental affected status, and maternal positive history as independent variables most adequately explains the patterns in the families.

A study of the neurodevelopmental characteristics of Sudden Infant Death Syndrome siblings strongly suggests genetic involvement. Research suggests that the increased familial incidence is possibly indicative that the disorder is genetically inherited (Chapman, 1991). Furthermore,, indirect or presumptive evidence for genetic factor involvement in Attention Deficit Disorder and Sudden Infant Death Syndrome appears to be apparent. The genetic hypothesis is suggested by association between Attention Deficit Hyperactivity Disorder, Tourette's Syndrome and factors which we have reason to presume may be linked to central nervous system integrity, familial patterns, early risk events, minor physical anomalies, infrabehavioural signs, as well as the lack of psychosocial factors to explain these disorder (Chapman, 1991).

Therefore, it appears that the neuropsychological disorders reviewed above have several common symptoms, the most interesting of which is attention deficit, or hyperactivity, which is a disorder of arousal. It is hypothesized that the above-mentioned disorders are caused by a pervasive neurological deficit, and it is suggested that the gene responsible for the facilitation of inhibition and arousal of sensory and motor activity is the cause of the disorders that are under investigation. Co-transmission analyses within families can help to clarify which associated phenotypes are intrinsically related. The more closely related the defining symptoms are to the underlying mechanisms of the disorder, the more informative the genetic analyses will be. Once the phenotype is provisionally defined, the first step in the search for genetic influences is a test of familiarity, that is, whether there is increased risk among relatives of a proband that may fall off proportionally with the degree of relationship.

Most important is the idea that these different kinds of analyses form a sequence of steps toward a final

genetic understanding of a complex disorder and that one can use this somewhat oversimplified sequence to evaluate the current state of knowledge about genetic influences in Sudden Infant Death Syndrome, Attention Deficit Disorder, Attention Deficit Hyperactivity Disorder, and Tourette's Syndrome. Genetic involvement in paediatric neuropsychological disorders will be covered in the next Chapter. As an important aspect is the definition of the phenotype, the research on Tourette's Syndrome and Attention Deficit Hyperactivity Disorder provides an interesting example of how family studies can help determine which symptoms are intrinsic to a phenotype and which are simply associated with it.

CHAPTER THREE

CHILDREN AT RISK : A DEVELOPMENTAL NEUROPSYCHOPATHOLOGY

3.1   Introduction

At present, little is known about what proportion of paediatric neuropsychological disorders are genetically influenced, which are polygenetic, that is, influenced by a large number of genes acting in an equal and additive fashion, and which have major gene effects. There is evidence for major gene effects on Attention Deficit Disorder, and on Tourette's Syndrome (Pennington and Smith, 1988). What is of note is that the predominance of the polygenic model as an explanation for genetic influences on complex phenotypes has been challenged by recent advances in molecular genetics. In the sphere of behaviour, several complex disorders, including bipolar illness and Alzheimer's disease have been shown by linkage analysis to be associated with major gene transmission, specifically with autosomal dominant transmission (Pennington and Smith, 1988).

Linkage analysis is a statistical method for testing whether two genes segregate together in a non-random fashion, which would indicate that they are located close together on the same chromosome. Furthermore, by determining which genes are linked to each other and are unlinked to others, the relative location of the genes on the chromosomes can be mapped. "Chromosome walking" can refine the localization and, ultimately, the gene itself can be isolated and read so that its biological effects can be understood (Gershon et al, 1981).

Linkage analysis can be applied to the study of behavioural disorders because the determination that a disorder is linked to a known gene implies that the disorder itself is significantly influenced by a specific gene. In addition, the existence of more than one gene producing the disorder, genetic heterogeneity, can be detected through linkage analysis because different genes have different positions on the chromosomes (Pennington and Smith, 1988).

Many people are disturbed by the idea that genes can influence behaviour. Genes are merely chemical structures. However, encoded in these structures are the messages that enable genes to do their extraordinary job of reliably replicating themselves and controlling development (Plomin, Defries & McClearn, 1980). Genes are blueprints for the assembly and regulation of proteins, which are the building blocks of our bodies, including the nervous system. Genetic differences can account for a substantial portion of individual variation in many important behaviours.

The localization of a gene or genes for the neuropsychological disorders under discussion would provide a clear answer to the question about the range and possible subtypes of the phenotype involved. It would eventually lead to the defining of the underlying gene product.

3.2 Sudden Infant Death Syndrome

3.2.1 Apparent Polygenetic Abnormality

Studies of familial aggregation have been consistent with potential genetic transmission of Attention Deficit Hyperactivity Disorder and Attention Deficit Disorder. Probands have been identified on the basis of diagnosis of disorders such as dyslexia. When the incidence of these disorders for direct relatives of probands is compared with the incidence for relatives of controls, the typical result is a higher incidence for the relatives of probands (Decker & Defries, 1980). Morrison and Stewart (1971)and Cantwell (1975) found that families of hyperactive probands had higher incidences of alcoholism, sociopathy and hysteria than families of control subjects. In addition, fathers of hyperactive children were more likely to report themselves as being hyperkinetic, than fathers of controls.

A genetic etiology in some instances is possible because of the pronounced clustering on several instances within the same family, and an obvious increase in the prevalence of psychopathology among patients of Sudden Infant Death Syndrome siblings manifesting Attention Deficit Hyperactivity Disorder characteristics. Two studies documenting the familial clustering of dyslexia are those by Hallgren (1950) and Frisk et al, (1957). Frisk et al (1957) reported that 65% of parents or near relatives of teen-aged dyslexics were themselves dyslexic. The overlap with Attention Deficit Hyperactivity Disorder becomes apparent due to the prevalence of clumsiness, enuresis, lability,sleep disturbance, and distractibility among the affected group (Rie & Rie, 1980). It appears that the putative mode of genetic transmission is probably polygenetic. The reason for this assumption is that the gene does not "breed true", that is, breed 100% predictably. Abnormality appears to be transmitted from parent to child, but its manifestations vary. In families who have experienced the death of an infant from Sudden Infant Death Syndrome, one sometimes sees different patterns in the surviving offspring. One child may manifest symptoms of classical Attention Deficit Hyperactivity Disorder and the other may be merely clumsy (Pasaminick & Knobloch, 1966). Similarly, the parents of Attention Deficit Hyperactivity Disorder and Sudden Infant Death Syndrome infants appear to have a heterogeneous group of psychiatric difficulties. This failure to "breed true", while at variance with simple classic Mendelian principles, is compatible with principles involving multiple interacting genes, polygenetic transmission (Wender, 1970).

The risk of Sudden Infant Death syndrome in the general population of South Africa is 2/1000

(Padayachee, 1989) but is increased tenfold in surviving twins of Sudden Infant Death syndrome victims is twentyfold in surviving twins, independent of zygosity (Arsenault, 1980). This data suggest either genetic factors in these families, or a powerful environmental influence on intrauterine or extrauterine development. Several researchers have studied parents and siblings of Sudden Infant Death Syndrome victims with mixed results. Zwillich (1980) found no significant difference in the ventilatory response during the breathing of carbon dioxide in parents of Sudden Infant Death Syndrome victims and control parents. Schiffman (1980) reported a decreased response in Sudden Infant Death Syndrome parents. Comparison of the two studies showed that Sudden Infant Death Syndrome parents had similar responses but the controls in Schiffman's study had a brisker response. Furthermore, Schiffman reported an increased ventilatory response to carbon dioxide during inspiratory loading in controls and a decrease in Sudden Infant Death Syndrome parents. Zwillich's study found no change in ventilatory response to hypoxia. Kanarek et al (1981) found no difference in the ventilatory response to carbon dioxide, or to hypoxia in parents of Sudden Infant Death Syndrome infants.

Siblings of Sudden Infant Death Syndrome victims show an increase in periodic breathing during sleep when studied at home, but less short apnea and a higher respiratory rate when studied in the laboratory (Hoppenbrouwers, Hodgman et al, 1980). Once more the results of studies of family members of Sudden Infant Death Syndrome victims are in conflict. The difference in results may be ascribed to the different environments in which the studies were done. Consequently, no data in support of a genetic component of Sudden Infant Death syndrome is available. Although there is an increased incidence of Sudden Infant Death Syndrome in some families, there is no evidence that it is a genetically transmitted anomaly rather than a deficit in the intrauterine or extrauterine environment.

3.3   Vertical Transmission of Attention Deficit Hyperactivity Disorder

Several studies have provided evidence that Attention Deficit Hyperactivity disorder may be transmitted within families. Twin and adoption studies suggest that this familial clustering may be due to genetic factors. Pauls et al (1991) support the hypothesis that there is a strong familial clustering for Attention Deficit Hyperactivity Disorder. The observed patterns suggest that vertical transmission of the disorder occurs and that the sex difference observed in the population prevalence might be explained by a threshold effect. Logistic analyses indicate that a model that includes sex of the proband, parental affected status, and maternal positive family history as independent variables most adequately explains the patterns in the families. These analyses provide the strongest statistical evidence to date for the vertical transmission of Attention Deficit Hyperactivity Disorder (Pauls, Shaywitz et al, 1991).

Evidence of a biological basis for Attention Deficit Hyperactivity Disorder might come from the studies

of relatives of Attention Deficit Hyperactivity Disorder children, to see if there is a consistent pattern of disorders associated with this syndrome, or if hyperactivity "breeds true". Morrison and Stewart (1971) first identified a possible relationship between hyperactivity and alcoholism, finding that a higher proportion of fathers (20%) and mothers (5%) of hyperactive children were alcoholics, compared with 10% of fathers and none of the mothers of the controls. A later study (Morrison & Stewart, 1973) showed that adoptive parents of hyperactive children did not have a higher prevalence of alcoholism, hysteria, or sociopathy. Cantwell (1972) also found increased prevalence rates for alcoholism, sociopathy, and hysteria in the parents of the hyperactive children.

To separate adverse environmental effects from genetic influence, it is useful to examine offspring who have been adopted. In the only such study, Cantwell (1975) compared the adopting families of hyperactive children with biological families of hyperactive children. The biological fathers had a much higher incidence of alcoholism and sociopathy, and biological mothers had a considerably higher incidence of hysteria than did the adopting parents or controls. Studies have compared monozygotic and dizygotic twins for the hereditability of activity. Lopez (1965) reported 10 sets of twins aged between 5 and 12 years, one of whom was considered to be hyperactive; four parts were monozygotic and six were dizygotic. While the dizygotic group had concordance in only one of six parts and the monozygotic group was completely concordant, the results cannot be usefully interpreted because four of the dizygotic twin pairs were of different sexes. The genetic data suggests a relationship between childhood Attention Deficit Hyperactivity Disorder and later alcoholism, sociopathy and hysteria. Attention Deficit Hyperactivity disorder has frequently been linked to parental psychopathology. Many early family studies of children with the "hyperactive child syndrome "found a high rate of Antisocial Personality Disorder, hysteria, and alcoholism in the parents of hyperactive children (Cantwell, 1972; Morrison, 1980; Morrison & Stewart, 1971). Several recent studies that have controlled for the frequent co-occurrence of Attention Deficit Hyperactivity Disorder and Conduct Disorder have found that parental Antisocial Personality Disorder and parental substance abuse are highly prevalent in families of children with Conduct Disorder, but not in families of children with Attention Deficit Hyperactivity Disorder (Beiderman, Muner et al, 1987; Reeves, Werry, et al,1987; Stewart, de Blois et al, 1980). A higher rate of Attention Deficit Hyperactivity Disorder in the parents and other biological relatives of children with Attention Deficit Hyperactivity Disorder was reported (Barkley, Du Paul et al, 1990; Beiderman et al, 1986; Beiderman et al, 1987). In addition, parents of children with Attention Deficit Hyperactivity Disorder have been reported to have more attention problems than control parents (Alberts-Corush, Firestone et al, 1986). Therefore, there is preliminary evidence that parents and other biological relatives of children with Attention Deficit Hyperactivity Disorder show many of the same difficulties as these children.

The possibility of a familial transmission of Attention Deficit Hyperactivity Disorder is important for theories of the etiology of the disorder. Barkley et al (1990) found that children with Attention Deficit Hyperactivity disorder were significantly more likely to have both maternal and paternal relatives with a childhood history of Attention Deficit Hyperactivity Disorder. There was also a higher rate of aggression and substance abuse in the childhood histories of maternal relatives of children with Attention Deficit Hyperactivity Disorder than for the relatives of control children. Interestingly, these differences were found only for children with both Attention Deficit Disorder and hyperactivity, but not for children with Attention Deficit Disorder without hyperactivity, who were found to have a higher rate of anxiety disorders in maternal relatives. Children with Attention Deficit Hyperactivity Disorder were significantly more likely to have a mother, a father, one relative, or two relatives, who exhibited more than three Attention Deficit Hyperactivity Disorder symptoms during childhood (Frisk, Lahey, et al, 1991). Frisk et al's (1991) research findings suggest that biological relatives of children with Attention Deficit Hyperactivity Disorder and Conduct Disorder have different childhood histories of behaviour problems. Specifically, mothers, fathers, and all first degree relatives of children with Attention Deficit Hyperactivity Disorder were significantly more likely to have histories of behaviour problems associated with Attention Deficit Hyperactivity Disorder, eg. inattention, impulsivity, and motor hyperactivity, but not histories of anti-social behaviour, or childhood substance abuse. However, in contrast to the results of Barkley et al, (1990), attention deficits with and without hyperactivity, were similarly associated with a family history of Attention Deficit Hyperactivity Disorder.

Family-genetic studies have consistently found relatives of boys with Attention Deficit Disorder or Attention Deficit Hyperactivity Disorder to be at greater risk for Attention Deficit Disorder and other psychiatric disorders than relatives of boys without Attention Deficit Disorder (Beiderman, Muner et al, 1986; Beiderman Faraone, et al, 1990; Morrison & Stewart, 1971; Cantwell, 1972). The familial transmission of Attention Deficit Hyperactivity Disorder among families with a son who has the disorder provides external validation for the diagnosis in boys and suggests genetic influences in the disorder. Faraone, Beiderman et al (1991) found that separated or divorced parents were more common among the girls with Attention Deficit Disorder. The relatives of girls with Attention Deficit Disorder also had higher risks for one or more antisocial disorders, major depression, and anxiety disorders. Their relatives were more likely to have required extra help in school and to have been placed in special classes.

Further examination of the differences in risk for Attention Deficit Disorder by gender of relatives revealed that male relatives of girls had a higher risk for substance use disorders than female relatives. Research findings indicate that Attention Deficit Disorder is highly familial in clinically referred children with Attention Deficit Disorder, with and without hyperactivity. In addition, their families are

also at high risk for anti-social disorders, major depression, anxiety disorders, and school dysfunction. The similar pattern of psychiatric disorders in the families of girls and boys with Attention Deficit Disorder suggests that familial etiological factors in Attention Deficit Disorder may not differentiate between the two genders.

3.4 Tourette's Syndrome

Recent genetic studies indicate that Tourette's Syndrome is transmitted as a hereditary trait in the same families, and that Chronic Multiple Tic Disorder seems to be a mild form of Tourette's Syndrome(Golden, 1978: Pauls, Cohen et al, 1981). Although chronic, multiple motor and phonic tics are usually the most prominent clinical features of Tourette's Syndrome, and represent the signs upon which the diagnosis of the disorder is currently based. Tics may also be accompanied by a variety of behavioural disorders. Studies have demonstrated a high incidence of obsessive-compulsive disorders, generally about 50% in Tourette's Syndrome patients (Frankel, Cummings et al, 1986; Pitman, Green et al, 1987). Pauls et al, (1986) studied the rates of Tourette's Syndrome, Chronic Tic Disorder and Obsessive Compulsive Disorder, in first degree relatives of Tourette's Syndrome probands, and found an increased rate of Obsessive Compulsive Disorder in a pattern suggesting that Obsessive Compulsive Disorder may be an alternate expression of the Tourette's Syndrome trait. This opinion is supported by segregation analysis of Tourette's Syndrome families which indicates that Obsessive Compulsive Disorder is etiologically related to Tourette's Syndrome and supports autosomal dominant inheritance with sex-specific penetrance and variable expression (Pauls, Leckman, et al 1986; Pauls, Pakstis et al, in press). When Obsessive Compulsive Disorder is considered an alternative expression of the putative Tourette's Syndrome gene, as described by Comings and Comings (1987a), penetrance estimates for females rise from 56%, when only Tourette's Syndrome or Chronic Tic Disorder is considered, to 70%.

About 50% of patients with Tourette's syndrome will show evidence of Attention Deficit Hyperactivity disorder, manifested by inattention, impulsivity, and hyperactivity (Kurlan, 1988). Comings and Comings (1984) inspected many Tourette's Syndrome family pedigrees and concluded that the Tourette's Syndrome genetic defect could be expressed as Attention Deficit hyperactivity disorder, without tics. However, the segregation analysis studies of Pauls and Leckman (1986) did not indicate an etiologic relationship between Attention Deficit Hyperactivity Disorder and Tourette's syndrome, as inclusion of Attention Deficit Hyperactivity Disorder as an alternative clinical expression of Tourette's Syndrome did not alter penetrance estimates, but resulted in an increase in the estimated phenocopyrate (Pauls, Leckman et al, 1986). Furthermore, Pauls et al (1986) found that the rate of Attention Deficit Hyperactivity disorder among relatives of probands with both Tourette's Syndrome and Attention Deficit Hyperactivity disorder was eight times higher than for probands with Tourette's Syndrome alone,

suggesting that the two traits segregate independently. The authors determined that the generally observed association between Attention Deficit Hyperactivity Disorder and Tourette's Syndrome may represent ascertainment bias, in that subjects with both problems are more likely to be referred for medical evaluation.

Many recent investigations have addressed the problem of a genetic predisposition in Tourette's Syndrome, but the precise genetics are unclear (Zausmer & Dewey, 1987) as it is sparse (Baraitser, 1982). However, the evidence is mostly in support of a major dominant gene, although there have been several variations on this theme. Convincing evidence for a genetic factor comes from twin data. Thus, there are several well-documented twin studies, which included 11 concordant monozygotic twin sets (Shapiro et al, 1978; Jenkins & Ashby, 1983; Waserman et el, 1983; Vieregge, 1987). Concordance rates for Tourette's Syndrome were 53% for monozygotic pairs, and 8% for dizygotic pairs. Price et al, (1984) concluded that although these concordances are consistent with genetic etiology, the fact that only 53% of monozygotic twins were concordant, suggested that non-genetic factors also play a role in the expression of Tourette's Syndrome. It was found in each case of disconcordant twins, the unaffected twin had a higher birth weight than the affected twin (Leckman et al, 1987).

It was therefore speculated that some pre-natal events or exposure such as maternal stress, anti-emetic medication or other unknown agents may lead to changes in the sensitivity of some dopaminergic receptors, and these could partially determine the eventual severity of the expression of the Tourette's Syndrome diathesis (Leckman et al, 1987). Furthermore, numerous family studies indicate that the relatives of probands with Tourette's Syndrome may present with either Tourette's Syndrome or motor or vocal tics only (Dunlap, 1960; Friel, 1973; Eldridge et al, 1977; Kidd et al, 1980; Baron et al, 1981; Pauls et al,1981; Kurlan et al, 1986). Moreover, some studies provide evidence that, within these families, chronic multiple tics and Tourette's syndrome are genetically related (Pauls et al, 1981; Pauls & Leckman, 1986).

The precise mode of transmission of Tourette's Syndrome is unclear, as is evidenced by the conflicting literature reports, thus Balthasar (1982) reviewed nine studies and proposed incomplete dominance as the most likely form of inheritance, while a recessive gene seems less likely. More recently, Devan (1984), Price et al, (1984) and Pauls and Leckman (1986) suggest the presence of a major autosomal dominant gene with varying penetrance. The family studies indicate that the Tourette's Syndrome gene may have a low (Comings & Comings, 1984a) or high penetrance (Pauls & Leckman, 1986). This difference of interpretation of the expression of the gene may, however, be due to the difference in diagnostic criteria for Tourette's syndrome, since the Yale Group (Pauls & Leckman 1986) use fairly stringent criteria, whereas the Duarte Group (Comings & Comings, 1987a) include many other disorders

within the Tourette's Syndrome spectrum; eg hereditary acrophobia, stuttering, panic attacks, mania, depression and schizoid behaviours. Comings and Comings (1986) further suggest the possibility of an X linked modifying gene to account for the increased evidence in males.

Recent studies have indicated that Tourette's Syndrome and Chronic Motor Tics show a familial concentration (Eldridge et al, 1977; Golden, 1978; Kidd et al, 1980; Shapiro et al, 1978), and in families of Tourette's Syndrome patients, Chronic Motor Tics occur as a milder manifestation of the same etiologic factors (Pauls et al, 1981). When Chronic Motor Tic and Tourette's Syndrome in the families of Tourette's Syndrome probands are considered, there is convincing evidence that susceptibility to Tourette's Syndrome and Chronic Motor Tic is transmitted vertically from generation to generation (Kidd et al, 1980; Pauls et al, 1981). The familial pattern can be explained by genetic models which incorporate both sex and severity differences (Kidds & Pauls, 1982). The evidence strongly supports the hypothesis of a major genetic component being involved in the etiology and transmission of the disorder and provides some indication concerning the pattern of transmission within the families. The results suggest a relationship between the transmission of the disorder and the sex difference observed in the Tourette's Syndrome population (more males than females affected) and further suggest that Chronic Motor Tic is indeed a milder form of the same underlying susceptibility to the disorder.

3.4.1   Conclusion

In conclusion, there has recently been some consensus of opinion that Tourette's Syndrome is probably inherited by an autosomal single dominant gene with varying penetrance. There have also been suggestions from both family and genetic studies that the same gene may be expressed as an Obsessive Compulsive Disorder (Montgomery et al, 1982; Pauls & Leckman, 1986; Pauls et al, 1986a, b; Kurlan et al, 1986), yet there is not agreement as to whether or not the gene is expressed as solely an attention deficit disorder with hyperactivity (Comings & Comings, 1984; Kurlan et al, 1986; Pauls et al, 1986c) and only scant evidence for the gene being expressed as agoraphobia with panic attacks (Comings & Comings, 1987b).

The recognition of a specific inheritance pattern for Tourette's Syndrome and the identification of large kindreds affected by the illness have raised hopes that the application of pedigree linkage analysis, using modern recombinant DNA technology, may be able to identify a genetic marker linked to the disease (Pauls, Pakstis et al, 1990; Kurlan, Behr et al, 1986).

3.5 Assortative Mating

In contrast to inbreeding, assortative mating is much more common and is character-specific. Thus, individuals sort themselves into mating couples on the basis of certain phenotypic characteristics (Plomin, DeFries, McClearn, 1980). Like inbreeding, assortative mating affects only genotypic frequencies, not frequencies of alleles. If we consider the influence of a single locus on a trait for which positive assortative mating occurs, assortative mating, like inbreeding, reduces heterozygosity. Homozygotes tend to mate with homozygotes, and some heterozygous individuals in each generation have homozygous offspring. However, for individuals influenced by genes at many loci, assortative mating will not greatly reduce heterozygosity. However, assortative mating for such individuals may substantially increase genotypic variability. Positive assortative mating thus increases the variances, in the sense that the offspring differ more from the average than they would if mating were random. Among behavioural individuals, most personality-rating correlations between mates are found in the 0.01 to 0.020 range, comparable to values observed for the physical characters (Van den Berg, 1972). Correlations for cognitive measures, most notably intelligence quotient, have been thought to be much higher, of the specific cognitive abilities (such as memory, spatial ability, verbal ability, and perceptual speed), verbal ability seems to show the most assortative mating (Johnson et al, 1978). This theory implies that individuals who carry the behavioural gene that results in Tourette's Syndrome, Attention Deficit Disorder, Attention Deficit Hyperactivity Disorder, and Sudden Infant Death Syndrome may be attracted to one another, thus strengthening the gene. Although the correlations are not large, assortative mating can still greatly increase genotypic variability in a population because it affects accumulate generation after generation. Assortative mating changes genotypic frequencies without affecting frequencies of alleles (Plomin, DeFries & McClearn).

Although genetic factors are now clearly recognized as those most important for the development of Tourette's Syndrome and related tic disorders, investigators continue to search for underlying neurochemical and neuroanatomic disturbances that may be manifestations of the gene defect and involved in the pathogenesis of the disorder.

3.6 Chromosomes and Genetic Variability

Mendel's elements of inheritance are carried on chromosomes and they assort independently through the process of meiosis. Crossing over contributes even more to genetic variability by providing for recombination of genes at different loci on the same chromosome. Meiosis is responsible for the fact that we resemble our parents in that we receive one chromosome of each homologous pair from each of them. However, meiosis and crossing over guarantee that the offspring are genetically unique

(Plomin, DeFries & McClearn, 1980).

Behavioural genetic theory is phrased in terms of static structural genes (DNA that codes for peptides), which are viewed as constants, rather than in terms of the dynamic aspects of genetic coding that regulate developmental change. Exciting discoveries such as "exon shuffling" within "split genes", and "jumping genes", have changed the old operon model of gene regulation. Through these dynamic mechanisms of gene coding, minor genetic events can generate extremely complex organizational changes within hierarchical multigene systems (Hunkapiller, Huang et al, 1982). It is a strongly held belief that genetic influences are locked on at full throttle at conception. However, genes do turn on and off during development (Davidson, 1976). There is an equally mistaken interactionist theory that the separate effects of heredity and environment cannot be analyzed. From a normative perspective, both genes and environment are necessary for an organism to develop (Plomin, 1983). From the perspective of individual differences, however, either genes or environment or both can contribute to observed differences among individuals. Sandra Scarr and Richard Weinberg (1980) stated "One cannot assess the relative impact of heredity and environment on intelligence per se, because everyone must have both a viable gene compliment and an environment in which the genes can be expressed over development. No genes, no organism; no environment, no organism. Behavioural differences among individuals, on the other hand, can arise in any population from genetic differences, from variation among their environments, or both".

3.6.1   Quantitative Genetics

Quantitative genetics considers multifactorial effects (multiple genetic and environmental sources of variation) rather than single-gene influences (Plomin, 1983). Characters influenced by only one gene are often called Mendelian, because they show the classical segregation ratios described by Mendel. Although there are many examples of the effects of single genes on behaviour, most of these interrupt the organisms normal course of development (Plomin, DeFries & McClearn 1980). However, the normal range of behaviour variation is more likely to be orchestrated by a system of many genes. Sir Ronald Fisher (1918) put the finishing statistical touches on a multifactorial model that indicates that the combined influences of many genes, each with a small effect, produce substantial genetic variance. Hall (1977) and Ward (1977) state that normal behaviour is generally influenced by many genes, even though a mutation of any one of these genes can disrupt the normal process of development.

Full siblings who have both parents in common are twice as similar genetically as half-siblings, with only one parent in common. If genes influence a particular behaviour, then the double genetic similarity of full siblings should make them more similar for that behaviour than half-siblings. Parents and their

offspring share one half of their additive genetic variance. Offspring cannot obtain a chromosome pair from one parent. Therefore, although dominance may contribute to the phenotypes of parent and offspring, this genetic factor will not be shared by them (Plomin, DeFries, McClearn, 1980). Assortative mating is another factor that contributes to genetic covariance among relatives. Assortative mating adds to the genetic similarity between parents and their offspring, as well as between siblings (Jensen, 1978). If assortative mating exists, a correlation between mothers and their children will include not only the genetic similarity between the mothers and their children, but also some part of the genetic similarity between the children and their fathers. Siblings, like parents and their offspring, share half of the additive genetic variance that influences a character (Plomin, DeFries, & McClearn 1980). For any behaviour, there are likely to be a wide range of individual differences. These phenotypic differences may be caused by environmental experiences, as well as genetic differences.

Specific cognitive abilities are also influenced by genetic factors. The intelligence quotient does not tell the whole story of intelligence. Although there is a general factor of cognitive functioning, there are also specific abilities. The number of these specific abilities depends on the level of analysis. These abilities range from two general abilities, verbal and performance factors through the 6 to 12 group factors measured by L.L. Thurstone. Although these specific abilities tend to be modestly correlated with one another, lending support to the idea of general intelligence, they are sufficiently different to permit a more fine-grained analysis of cognitive functioning (Plomin, DeFries & McClearn, 1980). Research by Plomin et al (1980), using 15 tests for the measurement of specific abilities yielded four group factors; verbal, (including vocabulary and fluency), spatial visualizing and rotating objects in two and three dimensional space, perceptual speed (simple arithmetic and number comparisons), and visual memory (short-term and longer-term recognition of line drawings). These findings suggest that the genetic and environmental influences salient to specific cognitive abilities are neither very broad nor are they peculiar in their influence. However, it appears that several sets of genetic and environmental influences correspond to the phenotypic factors. These findings indicate that these human behavioural data suggest that genetic and environmental correlations are correlated.

Adoption studies provide the most convincing demonstration of the genetic influence on complex human behaviours. Scarr and Weinberg (1980) observed that shared family environment relative to cognitive abilities, scholastic achievement, personality, interests, and attitudes, fades to negligible importance after adolescence. Furthermore, adopted children resemble their biological mothers more than they resemble their adoptive parents who have reared them from birth. Plomin and DeFries (1980) found that individual differences in the first years of life are generally unpredictable, although some significant genetic and family environmental influences have been detected. However, McCall (1981) maintains that shared family environment is much less important than previously thought. Salient environmental

influences, whatever they may be, operate in such a manner as to make children in the same family as different from one another as from children in different families.

3.6.2   Genetic Influences on Behavioural Phenotypes

At present it is not known what proportion of behavioural phenotypes are genetically influenced, which of these are polygenic, that is, influenced by a large number of genes acting in an equal and additive fashion, and which have major gene effects. In the domain of behaviour, several complex disorders have been shown to be associated with major gene transmission, specifically, with autosomal dominant transmission (Pennington & Smith, 1988). There is no a priori reason why major gene effects will not be found for Attention Deficit Hyperactivity Disorder and Tourette's Syndrome, and so the issue is an empirical one. Linkage analysis is a statistical method for testing whether two genes segregate together in a nonrandom fashion, which would indicate that they are located close together on the same chromosome. In addition, by determining which genes are linked to each other, and are unlinked to others, the relative location of the genes on the chromosomes can be mapped. "Chromosome walking" can refine the localization and, finally, the gene itself can be isolated and read so that its biological effects can be understood (Pennington & Smith, 1988).

The application of linkage analysis to the study of behavioural disorders because the determination that a disorder is linked to a known gene indicates that the disorder itself is significantly influenced by a single gene. Furthermore, the existence of more than one gene producing the disorder (genetic heterogeneity) can be detected through linkage analysis because different genes have different positions on the chromosomes. Tourette's Syndrome is a fairly prevalent (approximately 2% for the broadly defined phenotype) familia disorder of childhood that represents a major public health concern because of its impact on school adjustment and behaviour. There is a preponderance of affected males, with the male: female ratio ranging from 3-4,7:1 (Corbett, Matthews et al, 1969; Erensbuerg, Cruse & Rothner, 1986). However, there is evidence for autosomal dominant transmission. It is unclear at present whether there is a specific cognitive phenotype associated with Tourette's Syndrome and issues of phenotype definition have been more critical in arriving at an understanding of the manner of genetic transmission in Tourette's Syndrome.

There is evidence of comorbidity with a wide range of other behavioural phenotypes in some Tourette's Syndrome populations, including chronic tics, Obsessive Compulsive Disorder, Attention Deficit Disorder, Attention Deficit Hyperactivity Disorder, discipline problems, and even dyslexia (Pennington & Smith, 1988). The crucial question is, which of these associations are artifactual,, and which are alternative expressions of the same genetic factors that produce Tourette's Syndrome. Because genetic

syndromes especially those with dominant inheritance, can produce alternative manifestations, that is pleiotropy, such circumstances may exist as regards Tourette's Syndrome. Family studies have indicated that Tourette's Syndrome is familial, but have not pointed out a definite mode of inheritance. However, it was observed that the relatives of patients with Tourette's Syndrome had a higher incidence of chronic tics and this was concluded to be as alternate expression of the Syndrome (Pauls, Cohen et al, 1981). Recently, the phenotype of the Tourette's Syndrome gene has been further expanded. Comings and Comings (1985) in their study of 250 Tourette's Syndrome patients in their clinic, stated that 61% had significant discipline problems and/or problems with anger and violence, and that 32% (45% of female and 29% of male subjects) had Obsessive Compulsive Disorder.

These problems were noted with the onset of tics and were sometimes relieved by the same medication that suppresses the tics. Pauls and Leckman (1986) were able to show that Obsessive Compulsive Disorder is an alternate manifestation of the Tourette's Syndrome gene by performing co-transmission analysis within families of Tourette's Syndrome probands. They compared genetic models based on two definitions of the Tourette's Syndrome phenotype (Tourette's Syndrome and/or Chronic Tic Disorder & Obsessive Compulsive Disorder) and also tested the null hypothesis of no genetic transmission. They found that the model that included individuals with Obsessive Compulsive Disorder as gene carriers provided the best fit to the observed family data. Interestingly, more female subjects had Obsessive Compulsive Disorder, which increased the estimated penetrance of the Tourette's Syndrome gene in females from a previously estimated 0.30 (Comings & Comings,1984) to 0.70. The penetrance in males was found to be 1.0. The mode of inheritance was autosomal dominant, with only 10% of cases being phenocopies, that is, produced by a different mechanism (Pennington & Smith, 1988).

The large proportion of Attention Deficit Hyperactivity Disorder found in many Tourette's Syndrome samples suggests that Attention Deficit Hyperactivity Disorder might also be part of the Tourette's Syndrome phenotype. Comings and Comings (1984) proposed that Attention Deficit Hyperactivity Disorder might be the sole manifestation of the Tourette's Syndrome gene. They presented several pedigrees in which relatives of Tourette's Syndrome patients had Attention Deficit Hyperactivity Disorder; however, it was not reported whether Attention Deficit Hyperactivity Disorder alone was increased in relatives of Tourette's Syndrome patients. The presence of Attention Deficit Hyperactivity Disorder in the Tourette's Syndrome sample was found to be related to the severity of the Tourette's Syndrome, so an alternate interpretation of their findings could be that the behavioural problems seen in Tourette's Syndrome, especially in severe cases, can produce a phenocopy of Attention Deficit Hyperactivity Disorder (Pennington & Smith, 1988). A study by Pauls, Hurst et al, (1986) provided evidence against the hypothesis that Attention Deficit Hyperactivity Disorder alone can be a manifestation of the Tourette's Syndrome gene. When families of probands with Tourette's Syndrome

and Attention Deficit Hyperactivity Disorder were compared with families of probands with Tourette's Syndrome alone, the incidence of Tourette's Syndrome in relatives was found to be the same in both groups, but the incidence of Attention Deficit Hyperactivity Disorder in relatives was 8 times higher in the families of probands with both Tourette's Syndrome and Attention Deficit Hyperactivity Disorder. Furthermore, in families with both Attention Deficit Hyperactivity Disorder and Tourette's Syndrome, the two disorders were found to segregate independently (Pennington & Smith, 1988). This suggests that familial Attention Deficit Hyperactivity Disorder has a separate genetic mechanism, but it is still possible that severe Tourette's Syndrome can manifest with Attention Deficit Hyperactivity Disorder symptoms.

The cognitive characteristics of children with Tourette's Syndrome have been examined to see if there is a consistent pattern of deficit. Several studies have found a higher frequency of verbal IQ-performance, IQ discrepancies on the Wechsler Intelligence Scale for Children-Revised and poor performance on arithmetic on the Wide Range Arithmetic Test subtest (Bernstein, King & Carroll. 1983; Ferrari, Matthews & Barrabas, 1984; Incagnoli & Kane, 1981). However, there is not yet strong evidence of a specific cognitive phenotype in Tourette's Syndrome. Two other studies found more problems with behaviour and attention in Tourette's Syndrome patients rather than distinctive test performance profiles (Hagin, Beecher et al, 1982; Harcherik, Carbonair et al, 1982).

The localization of a gene for Tourette's Syndrome would provide an answer to the questions about the range and possible subtypes of the Tourette's Syndrome phenotype. It would also lead eventually to defining the underlying gene product (Pennington & Smith, 1988). The linkage analysis of Tourette's Syndrome thus far have focused on chromosomes 18 because some patients with Tourette's syndrome had either a translocation or deletion involving chromosome 18 (Comings & Comings, et al, 1986; Donnar, 1987; Handelin, 1986). However, to date, nothing definitive has emerged, the protein dynorphia has been found to be lacking in the basal ganglia of Tourette's Syndrome patients (Handelin, 1986).

3.6.3   Autosomal Dominant Transmission

An autosome is any non-sex determining chromosome, of which there are 22 in man. The expected outcomes of certain crosses if a character is influenced by a single dominant gene is simply a matter of logic. By definition, only one allele will cause an individual to be affected. Therefore, the only way an offspring can be affected is if at least one of the parents is affected. Furthermore, about half of the offspring of an affected parent should be affected, because each offspring has a 50-50 chance of inheriting that allele from the affected parent. whether an affected parent is a heterozygote or a

homozygote can be determined by studying the parents' parents. If an affected individual has only one affected parent, then the individual must be heterozygous. Half of the offspring of matings between affected heterozygotes and unaffected individuals are likely to be affected, Three quarters of the offspring will be affected in matings between two affected heterozygotes. All the offspring of an affected homozygote parent will be affected.

Many genetic defects are single-gene, recessive characters, but dominant ones are rare. Huntington's chorea, a well-known neural disorder, is caused by a single dominant gene. Huntington's disease is characterised by loss of motor control, and progressive deterioration of the central nervous system. When this condition was traced through many generations of pedigrees, a consistent pattern of transmission was observed. Most afflicted individuals had a parent who was also afflicted and approximately half of the children of an affected parent eventually develop the disease (Plomin, DeFries & McClearn, 1980).

3.7   Conclusion

Recent genetic studies indicate that both Chronic Tic Disorder and Tourette's syndrome are transmitted as hereditary traits in the same families and that Chronic Tic Disorder seems to be a milder form of Tourette's syndrome (Kurlan, 1989). Transient Tic Disorder appears to also be part of the clinical spectrum of Tourette's Syndrome and a possible expression of the same genetic defect. A high incidence of Obsessive-Compulsive Disorder has also been found among Tourette's Syndrome Children. Pauls et al (1986) suggest that Obsessive-Compulsive Disorder may be an alternate expression of the Tourette's Syndrome trait. This notion is supported by segregation analysis of Tourette's Syndrome families which indicates that Obsessive-Compulsive Disorder is etiologically related to Tourette's Syndrome and supports autosomal dominant inheritance with sex-specific penetrance and variable expression (Pauls, Leckman et al, 1986).

About 50% of patients with Tourette's Syndrome will show evidence of Attention Deficit Hyperactivity Disorder, manifested by inattention, impulsivity, and hyperactivity (Kurlan, 1988). Comings and Comings (1984) inspected many Tourette's Syndrome family pedigrees and concluded that the Tourette's Syndrome genetic defect could be expressed as Attention Deficit Hyperactivity Disorder without tics. However, the segregation analysis studies of Pauls and Leckman (1986) did not indicate an etiological relationship between Attention Deficit Hyperactivity Disorder and Tourette's syndrome, as inclusion of Attention Deficit Hyperactivity Disorder as an alternative clinical expression of Tourette's Syndrome did not alter penetrance estimates but resulted rather in an increase in the estimated phenocopy rate. Pauls et al (1986) found that the rate of Attention Deficit Hyperactivity Disorder among

relatives of probands with both Tourette's Syndrome and Attention Deficit Hyperactivity Disorder was 8 times higher than for probands with Tourette's syndrome alone, suggesting that the 2 traits segregate independently.

Recent research among siblings of Sudden Infant Death Syndrome infants (Chapman, 1991) found that a significant number of the children were diagnosed as Attention Deficit Hyperactivity sufferers and that there was a higher rate of Attention Deficit Hyperactivity Disorder in the parents, particularly the fathers and grandfathers. There was also a higher rate of aggression and alcohol abuse in the childhood histories of paternal relatives of these siblings. The maternal relatives were found to have a higher rate of anxiety disorders (Chapman, 1991). These results point towards genetic involvement in Sudden Infant Death Syndrome.

The evidence for major gene influences on specific aspects of cognition and behaviour has increased considerably. Less is known about the neurological substrate of the disorders, but the specificity of some of the behavioural phenotypes argues for specific and differentiable neural mechanisms. It is quite possible that many genetic anomalies will have non-specific effects on the developing central nervous system, and will produce a general decrease in neuropsychological functioning. However, it appears that the neuropsychological disorders discussed above have several common symptoms, the most striking of which is hyperactivity, or more generally, a disorder of arousal which manifests in several different ways.

From an interactional perspective, it appears that children experience a group of problems that seem to cluster. These difficulties seem to exhibit genetic effects (Plomin, 1983). The etiology is not known but there is evidence of neurological involvement (Galaburda, cited in Silver, 1990). These deficits sometimes coexist, at times seem independent, and overlap substantially (Barkley, 1981; Rutter, 1983). They may be confined to a specific domain, as in reading problems, or may be pervasive, affecting academic and social learning, behaviour, and affective development.

Co-morbidity has become an important area of research in recent years, as studies reveal that high percentages of children with Attention Deficit Disorder/Attention Deficit Hyperactivity Disorder also suffer from other disturbances. Attention deficit disorders appear to be associated with a variety of other childhood psychiatric problems, and numerous psychiatric conditions can present as attention difficulties. This appears to be the case in the syndromes under investigation, as they all have attention deficit as a common symptom although there are other symptoms involved. There is considerable overlap of Attention Deficit Disorder/Attention Deficit Hyperactivity Disorder with other childhood disorders besides the ones discussed above. These include learning disabilities, oppositional defiant

behaviour, aggressive behaviour, mood disorders, particularly depression, anxiety disorders and substance abuse and personality disorders, particularly among adolescents and young adults. It therefore appears that these are a single condition which are expressed differentially. It is therefore hypothesized that these disorders may be the result of an underlying dysfunction in the inhibitory forebrain system controlling attentional processes in response to situational demands. However, specific criteria must be satisfied before we can conclude either that a phenotype is genetically influenced or that a known genetic alteration leads to a specific and consistent phenotype.

Contrary to Comings and Comings (1987a) proposal that the Tourette's Syndrome gene is one of the causes of Attention Deficit Disorder and that Attention Deficit Disorder is one of the pleiotrophic effects of the Tourette's Syndrome gene, a study needs to be undertaken to investigate whether Attention Deficit Disorder, Attention Deficit Hyperactivity Disorder, Tourette's Syndrome and the symptoms manifested by siblings of Sudden Infant Death Syndrome victims are not manifestations of a neurodevelopmental deficit that manifests in different ways. It was hypothesized that the abovementioned disorders were all caused by a pervasive neurological deficit or disorder. Hyperactivity appears to be a common symptom in the abovementioned disorders and it is suggested that the gene responsible for the facilitation of inhibition and arousal of sensory and motor activity is the cause of the disorders that are under investigation, and that these disorders are the pleitrophic effects of this gene.

It would be important to compare children with Attention Deficit Disorder, Attention Deficit Hyperactivity Disorder, Tourette's Syndrome, siblings of Sudden Infant Death Syndrome infants and normal children. This experimental design would allow comparisons to be drawn between the five groups and would indicate neurodevelopmental or neuropsychological deficits, particularly on a motor, attention, visual motor integration, planning and organization, visual perception, short-term memory and processing of information level.

As data obtained in a previous study indicated that subsequent siblings of Sudden Infant Death Syndrome may possibly exhibit neurodevelopmental dysfunction (Chapman, 1991), it would be necessary to make use of neuropsychological tests , as they tend to assess higher level cognitive function and skills (Rutter, 1981). A comprehensive data base encompassing demographic information, genetic background, pre- and perinatal events, developmental and social history, symptomatic survey, educational experiences and current areas of difficulty had already been covered in a previous study (Chapman, 1991), tests measuring various neurological functions should be used.

Perceptual, motor, and neuromaturational competence will be assessed using a battery of tasks with five groups of children with diagnosed disorders of Tourette's syndrome, Attention Deficit Disorder with

no known organic substrate, Attention Deficit Hyperactivity Disorder, siblings of Sudden Infant Death Syndrome infants, and a control group. The purpose of the study would be to determine how the five groups differentiate from each other on these measures.

CHAPTER 4

METHODOLOGY

4.1   Introduction

Until recently, the precursors of Sudden Infant Death Syndrome, as well as the causes, were obscure. As there is a lack of any satisfactory explanation for Sudden Infant Death Syndrome, various attempts have been made to document the conditions that could possibly create the basis of a "risk catalogue". The listing of symptoms and signs, particularly if utilized in a cumulative and significant fashion, may provide a valuable example in developing a logical model of, or hypothesis, concerning the origins of Sudden Infant Death Syndrome. (Protestos et al., 1973). Furthermore, any strategy of defense against Sudden Infant Death Syndrome must ultimately specify those conditions likely to be present in infants whose vulnerability demands concern. Although many theories have been postulated the mechanisms underlying Sudden Infant Death Syndrome are not yet fully understood.

The term Sudden Infant Death Syndrome is used when no perceptible condition or diagnosable ailment can be identified. The use of the term " syndrome" in identifying the cause of death is conjectural, or at least premature, because no constellation of underlying disease factors has yet been found (Burns and Lipsitt, 1991). Numerous hypotheses about the origin ofSudden Infant Death Syndrome have been proposed. A review of research on Sudden Infant Death Syndrome over the last 20 years indicates that Sudden Infant Death Syndrome research has followed a similar pattern to other complex physiological or medical problems (Valdes-Dapena, 1978).

Most of these hypotheses have been discarded, and research has been directed towards disfunctioning in more subtle areas such as neurophysiological mechanisms (Hoppenbrouwers and Hodgman, 1982; Valdes-Dapena, 1978; Kinney and Filiano, 1988). One of the leading hypotheses in Sudden Infant Death Syndrome research is that Sudden Infant Death Syndrome is caused by a subtle defect in brainstem neural circuits which control respiration and/ or cardiac stability during sleep. The unique age distribution, with a peak period between 2-4 months, and the risk factors of prematurity and low birth weight is indicative that maturational factors are involved (Kinney and Filiano, 1988).

The rapid development of the mammalian cortex in the first weeks of life, or the "brain growth spurt period" (Dobbing, 1974), accompanies the developmental progression at many levels of the system from reflexive to cortically mediated control (Parmelee & Sigman, 1983). McGraw (1939, 1943) documented the neuromuscular maturation, providing evidence that many of the infant's basic reflexes follow this progression from a stereotypical responding to a qualitatively different mode of "voluntary" responding.

116

A variety of other reflexes, which presumably reflect phylogenetic evolution, also progress from strong stereotypy to extinction and possible voluntary replacement .e.g. rooting, sucking, palmar grasp, etc).

There is strong support for qualitative changes in these reflexes as infants mature from reflexive to cortically mediated responding from many authors using differing measurement techniques and various operational criteria. Hunt and Brouillette (1987) stated quite convincingly that the most compelling hypothesis concerning the etiology is a deficiency in neuroregulation of cardiorespiratory control. They maintained that a "severe deficiency in asphyxic arousal responsiveness could be life threatening if the infant has been rendered incapable of responding effectively to progressive sleep-related asphyxia, whatever the cause" (p.670). They continued their argument pointing out that, in addition to impaired respiratory control, there could be other factors unrelated to respiratory control that could conspire with the underlying arousal deficit to result in Sudden Infant Death Syndrome.The control of respiration progresses in a specific pattern during the first months of life. At birth the infant's response to occlusion is controlled by the Hering-Breuer Inflation (HBI) reflex (Bodegard, Schwieler, Skoglund, & Zetterstrom, 1969; Sachis, Armstrong, Becker, & Bryan, 1982).

This reflex is related to inspiratory inhibition caused by sustained lung inflation. At approximately 38 weeks of postnatal age the HBI reflex diminishes and other responses dominated by thoracic spindle reflexes increase. The thoracic responses are measured by mean relative change in amplitude of the intraespheagal pressure of the breathing cycle during occlusion. These thoracic responses increase in strength, that is, the lungs expand less and less when threatened with occlusion from 30 to 42 weeks of postnatal age (Bodegard et al., 1969; Eichenwald & McCracken, 1969; Schweiler, 1968). The respiratory response to occlusion is considered in evaluating the infant's maturation from voluntary control because the thoracic spindle reflexes are considered to be sensitive to cortical mediation whereas the HBI reflex is not (Burns & Lipsitt, 1991). According to several authoritative researchers, it is possible that these thoracic defensive reflexes are under considerable influence by conditioning (Davis, 1974; Davis and Dobbing, 1974; Widdicombe, 1977) in contrast to the former defensive reflex (HBI) that is not cortically mediated. It is therefore assumed that under 1 month there may exist totally or predominantly reflexive respiratory responses to occlusion, whereas after 1 month , this reflexive system may be supplanted by reflexes that are modified by learning, and thus, can only be understood through the influence of cortical mediation. (Burns & Lipsitt, 1991).

McKenna (1986) maintains that our understanding of the parameters affecting switching from voluntary to involuntary control is inadequate. Bodegard et al. (1969) and Sachis et al.(1982) conjectured that there may be a relation between these developmental changes in respiratory control and the incidence of periodic breathing (apnea) found in premature and other infants in their first month of life. It is

theorized that a deficiency in arousal responsiveness secondary to delayed brain stem maturation may be responsible for this inability to respond effectively to progressive sleep related asphyxia (Naeye, 1980).

Arousal involves neural pathways originating in the reticular formation of the rostral pons, midbrain, and hypothalamus. The neorotransmitters that mediate arousal are not completely understood: acetylcholine, norepinephrine, serotonin, and dopamine have received most attention. The analysis of brainstem mechanisms in Sudden Infant Death Syndrome is hampered by imprecise knowledge of the neuronal populations and neurotransmitters/ neuromodulators involved in cardiorespiration and arousal (Kinney and Filiano, 1988). However, there is no single "resiratory or arousal centre", and that presently there are no specific morphologic or biochemical markers for respiratory or arousal-related brainstem neurons (Hoppenbrouwer and Hodgman, 1982).

The timing of Sudden Infant Death Syndrome with these physiological changes suggests that there is a critical period in central nervous system development during which the infant is vulnerable to neurogenic sudden infant death (Kinney and Filiano, 1988). Neuropathological studies in patients with central respiratory dysfunction and sudden death validate the theory that sudden death can result from brainstem lesions (Devereaux, Keene et al, 1973). The most consistently reported abnormality in the brainstem is subtle gliosis.This is a non-specific response to central nervous system injury after the second trimester, and accompanies almost all metabolic,toxic, infectious and other insults.

Gliosis occurs mainly in response to neuronal injury, and marks the site of neuronal loss (Kinney and Filiano, 1988). Brainstem gliosis appears to be present in some, but not all Sudden Infant Death Syndrome victims. This gliosis may mark a subset of Sudden Infant Death Syndrome victims with primary brainstem injury as a result of a presently unknown nonhypoxic insult, or a subset with recurrent apnea and secondary injury due to chronic hypoxia (Gilles, Bina, Sotrel, 1979).

The brainstem centres that control respiration are very close to structures that control other body functions, and so any fault impairing the respiratory control mechanisms might also possibly affect those other functions (Schwartz, 1987). Non- respiratory impairments are observed in some babies who succumb to Sudden Infant Death Syndrome. These impairments include abnormalities in temperature regulation, feeding and neurological reflexes. These abnormalities are often evident soon after birth. However, not much investigation has been done in correlating the various non-respiratory findings in Sudden Infant Death Syndrome infants with specific lesions of the brain (Naeye, 1980).

In order to conduct the study, fifty Causasian children between the ages of seven and fourteen were obtained. The control and experimental groups consisted of ten subjects in each. Three other groups

118

with ten children in each were used. These groups consisted of children who were diagnosed as suffering from Attention Deficit Disorder, Attention Hyperactivity Disorder, and Tourette's Syndrome. Diagnoses conformed to the criteria of DSM-111-R.

4.2 Subjects

Five groups, four experimental and one control group, consisting of ten Caucasian children in each, between the ages of seven and fourteen were assessed. The control group was described as "average" by their teachers. They were obtained from a local primary school, in a middle-class suburb. The control group was selected as representative of the general population, that is, not screened specifically for abscence of neurological deficits (Thoman, 1991). The control group consisted of children who were randomly chosen by their teachers. The remaining three groups consisted of ten children in each. These children were divided into one of three groups, namely Attention Deficit Disorder, Attention Deficit Hyperactivity Disorder, and Tourette's Syndrome. The ten children with Tourette's Syndrome had characteristic multiple motor and phonic symptoms with waxing and waning intensity, changing morphology, and temporary suppressibility. None were on medication at the time of testing.

The children with Attention Deficit Disorder exhibited impulsivity, short attention, poor concentration, frustration intolerance, and restless overactivity. The children with Attention Deficit Hyperactivity Disorder manifested signs of inattention, impulsivity, and motor hyperactivity. None of these children were on medication at the time of testing. The children with Attention Deficit Disorder,and Attention Deficit Hyperactivity Disorder were obtained from a local private remedial school. The children with Tourette's Syndrome were referred by several neurologists and/or paediatricians, who diagnosed the disorders. These children were diagnosed according to the DSM-111-R classification for this syndrome.

The subjects who were siblings of Sudden Infant Death Syndrome infants were used in a previous study (Chapman, 1991). They were obtained from The Cot Death Society and Compassionate Friends. The subjects in the other three groups were not as carefully matched, as suitable subjects were not readily available.

They had different socio-economic status, some were from single parent families and were generally representative of the general population, except for the neurological dysfunction. Due to the shortage of subjects diagnosed as suffering from Tourette's Syndrome and siblings of Sudden Infant Death Syndrome infants, the only exclusion criteria was if the subject had a below average intelligence quotient, or manifested any form of pre-psychotic behaviour.

The control group had to be matched to the Sudden Infant Death Syndrome sibling group as the

Tourette's Syndrome group consisted entirely of boys whereas the Sudden Infant Death Syndrome sibling group consisted of both boys and girls. The groups of subjects consisting of the Attention Deficit Disorder and Attention Deficit Hyperactivity Disorder sufferers were matched to the control and Sudden Infant Death Syndrome siblings groups for sex and age. However, the groups are representative of the general population in all other ways. All the subjects in the Attention Deficit Disorder, Attention Deficit Hyperactivity Disorder and the Tourette's Syndrome groups were selected according to the criteria stated in the DSM-111-R by a team comprising a Neurologist, Neuropsychologist, Occupational Therapist and Speech Therapist.

4.3   Instrumentation

The modalities to be assessed were, perception of environmental cues, processing of environmental cues, storage and motor performance. These included:
- memory for verbal information - memory functions,
- memory for non-verbal information - memory functions,
- processing of non-verbal stimuli - memory functions,
- visual spatial arrangements - processing,
- analytical ability, recognizing visual information - perception,
- global or gestalt thinking - processing, and
- social behaviour - performance.

A battery of neuropsychological tests were used as these tend to assess higher level cognitive function (Lezak, 1983). Screening tests of perceptual and motor functions were therefore used in the test battery. The test battery consisted of seven tasks to assess functioning in various areas. A test battery is defined as " a group of different tests designed to test a broad ability. The intercorrelations between the individual tests should not be too high, but the correlation between the overall result and the criteria should be higher than that of the individual test" (Eysenck et al 1972).

4.2.1   The Trail Making Test

This test, originally part of the Army Individual Test Battery (1944), is widely used in neuropsychological practice as part of a battery for detecting neuropsychological dysfunction. It is reported to be highly sensitive instrument in differentiating brain-damaged from non-damaged patients (Gordon, 1972; Lezak, 1983; Reitan, 1955, 1958). When used as a qualitative tool, it provides valuable information about the subject being tested (Reitan, 1958). Lezak (1983) mentions predictive value for occupational rehabilitation and more specific identification of deficits in neuropsychological function.

The test is simple, inexpensive and cost effective, being easily scored for quantitive analysis. The Trail Making Test was primarily designed to measure the adequacy of cerebral functioning, presumably frontal lobe functions, particularly conceptual tracking (Lezak, 1983).

The revised version of the Trail Making Test developed for children by Reitan (1955) was used. There is no standardized set of instructions for the use of the test with children. The test is made up of two Parts, Part A and Part B. Part A consists of a sheet of paper with circles printed in random arrangement on each side of the page. In the centre of each circle is a number which ranges from 1-8 for the practice sample on one side of the page, and from 1-15 for the test proper on the reverse side of the page, randomly placed. The subject is required to use a pencil to join the circles, in ascending order, as quickly as possible. Part B of the test is similar in structure to Part A, except that the circles in this case contain either numbers or letters. The test has numbered circles ranging from 1-8, and letters ranging from A-G, while the practice sample has numbers 1-4, and letters A-D. The testee is required to join the circles in ascending number-letter sequence (i.e. 1 to A, A to 2, 2 to B, and so on) ending with the number 8. The test performance is timed using a stop-watch.

The Trail Making Test was administered according to Reitan's (1956) instuctions for adults, with the following difference. When instructions for the test proper were given, only the first three circles of Part A (and the first four circles on Part B), were pointed to, in conjunction with the verbal instructions.

The examiner points out errors as they occur so that the child can always complete the test without errors and scoring is based on time alone (Lezak, 1983). When the number of seconds taken to complete Part A is relatively much less than that taken to complete Part B, the child probably has difficulties in complex- double or multiple- conceptual tracking, that is, visual scanning and tracking .Slow performances on one or both Parts A and B indicate the likelihood of brain damage, but in themselves do not indicate whether the problem is motor-slowing, incoordination, visual-scanning difficulties, poor-motivation, or conceptual confusion (Lezak, 1983). Walsh (1984) notes that apart from its general use as a speeded visuomotor tracking task, patients with frontal lobe lesions, particularly those with basomedial damage, have difficulty with the flexible control of inhibition needed for the task.

Wedding (1979) stated that data "failed to support the idea that the ratio of Trails A to Trails B is a useful indicant of lesion laterality". Therefore the use of this test to lateralise a lesion is highly questionable (Lezak, 1983). Lewinsohn (1973) found that performance on Trails A was predictive of vocational rehabilitation following brain injury. Visual scanning and tracking problems that show up on this test indicate how effectively the patient responds to a visual array of any complexity, his performance when he follows a sequence manually or when dealing with more than one stimulus or

thought at a time (Eson et al., 1978) or how flexible he is in shifting the course of an ongoing activity (Pontius and Yudowitz, 1980). It has the advantage of brevity and also yields a high proportion of correct identification (Korman & Blomberg 1963).

4.2.2   Differential Diagnosis/WAIS-R Digit Symbol subtest (Hart, Kwentus, Wade, & Hamer, 1987)

This symbol substitution task is taken from the Wechsler Adult Intelligence Scale. It consists of four rows containing in all, 100 small blank squares, each paired with a randomly assigned number from one to nine. Above these rows is a printed key that pairs each number with a different nonsense symbol. After a practice trial on the first seven squares, the child has to fill in the blank spaces with the symbol that is paired to the number above the blank spaces quickly as he can. After 90 seconds he is stopped. His score is the number of squares filled in correctly. The importance of speed must be stressed (Lezak, 1983). Kaplan (1977) uses the test to measure incidental learning. After the child has completed the 90 seconds, the test is folded under so that only the unmarked last row shows and the examiner requests the child to fill in from memory as many of the symbols as he can recall.

One point is scored for each square filled in correctly. Half credit is given for any reversed symbols. The ten samples are not included in the score. This test assesses visual-associative learning ability, psychomotor speed, visual-motor integration and co-ordination. Short-term memory for non-verbal information and processing of non-verbal stimuli which are functions of the right brain are assessed. This test is based on the assumption that the associative learning ability which is required to learn and is the relation between specific symbols and digits, is an indication of general intelligence (van Eeden, 1992).

This test is consistently more sensitive to brain damage than other Wechsler Adult Intelligence Scale Battery subtests in that its score is most likely to be depressed even when damage is minimal and to be the most depressed when other subtests are affected as well (Hirschenfang, 1960b). Digit Symbol tends to be affected regardless of the locus of the lesion, and therefore is of little use for predicting the laterality of a lesion (Lezak, 1983). The extensive work of McFie (1969 and 1975) demonstrated that the Digit-Symbol subtest of the Wechsler Scales shows impairment with lesions in virtually any location in a high proportion of cases.

4.2.3   The Complex Figure Test

A "complex figure" was devised by Rey (1941) to investigate both perceptual organization and visual

memory in brain damaged subjects. Osterrieth (1944) standardized Rey's procedure and obtained normative data from the performance of 230 normal children, with ages ranging from 4 to 15. The test consists of Rey's figure, two blank sheets of paper, and five or six coloured pencils. The testee is first instructed to copy the figure, which has been so set out that its length runs along the testee's horizontal plane. The examiner watches the testee's performance closely. Each time the testee completes a section of the drawing, the examiner hands him a different coloured pencil and notes the order of the colours. When completed, both the figure and the drawing are removed from the testee's field of vision. After 3 minutes, the testee is given a second sheet of paper and is asked to draw the design from memory.

Osterreith analysed the drawings in terms of the patient's method of procedure as well as specific copying errors. Seven procedural types were identified.(1) Testee begins by drawing the large rectangle and details are added in relation to it. (2) Testee begins with a detail attached to a central rectangle, or with a subsection of the rectangle, completes the rectangle, and adds remaining details in relation to the rectangle, (3) Testee begins by drawing the overall contour of the figure without explicit differentiation of the central rectangle and then adds internal details, (4) Testee juxtaposes details one by one without an organizing structure, (5) Testee copies discrete parts of the drawing with no semblance of organization, (6) Testee substitutes the drawing of a similar object, such as a boat or a house, (7) Testee produces an unrecognizable drawing.

Most examiners give both immediate and delayed recall trials of the figure. However, the amount of delay varies among examiners. Within the limits of an hour or so, the length of delay is apparently of little consequence (Lezak, 1983). As in the copy trial, the examiner should see that the order of the approach is recorded, either by giving the testee different colours to mark his progress, by drawing a numbered copy of what the testee draws, or - ideally - both. Performance on the two recall trials helps the examiner sort out different aspects of the constructional and memory disabilities that may contribute to defective recall of the complex figure (Snow, 1979; Wood et al., 1982). As the testee is not aware that he will be called upon to recall the figure subsequently, this allows for an examination of "incidental" memory, that is where the testee has made no definite intention to rememember.

A comparison of the scores for each trail will aid the examiner in determining the presence of visuographic or visual-memory defects, as well as their relative severity. Both left and right hemisphere dysfunctions may be assessed. A variety of cognitive processes, including planning and organizational skills and problem-solving strageties, as well as perceptual, motor, and memory functions may be assessed. Patients whose lesions are on the left tend to show preserved recall of the overall structure of the figure with simplification and loss of details. Patients with right-sided lesions who have difficulty copying the figures display even greater problems with recall (Milner, 1975; Taylor, 1969).

123

4.2.4   Pattern Completion

This subtest is taken from the Senior South African Intelligence Scale-Revised. Partially completed patterns have to be completed. Each item consists of three figures from which the testee has to deduce a pattern in order to draw the fourth figure. Free responses are required of the testee. The test consists of four practice examples which are taken into account in the scoring, and a further 15 items. The test is a non-verbal assessment of the processes underlying logical thinking. Accurate visual perception, concrete reasoning with the help of figures, concept formation and concentration are important in this test. The mental manipulation of the pattern parts comprises mainly synthesis in the easier items, whereas the more difficult items possibly also require verbalizing the observed relations (van Eeden, 1992). Synthesis and the verbalizing of observed relations is required. The test is based on the assumption that reasoning by means of analogies is an indication of general intelligence.

4.2.5   Story Memory

This subtest was taken from the Senior South African Intelligence Scale-Revised. The subtest is based on the Logical Memory Subtest of the Wechsler Memory Scale (Wechsler, 1945). The test consists of a short story that the examiner reads to the testee. The test begins with the instructions, "I am going to read a short story to you now. Listen carefully because when I finish I'm going to ask you to tell me as much of the story as you can remember". Upon reading the paragraph, the examiner instructs the subject," Now tell me everything you can remember of the story." The examiner should encourage the subject to recall as much as possible, by providing some structure for recall with appropriate questions.

The examiner should note where questioning began to keep track of spontaneous versus directed recall. The subtest is scored by awarding one point for every item recalled. The raw score was used. There are 43 items in the story. The test measures short- term auditory memory. Meaningful verbal matter is used to measure the testee's ability to attend in a relatively simple situation. It is assumed that logical memory (the ability to repeat, not necessarily verbatim, essential content/meaning) is an ability of which a certain minimum is required at every level of cognitive functioning. This test measures mainly left hemisphere functioning.

4.2.6   Digit Span

The Digit Span subtest used in the Wechsler Adult Intelligence Scale consists of two sections, namely Digits Forward and Digits Backward, which involve different mental activities and are affected differently by brain damage. Both tests consist of seven pairs of random number sequences that the

examiner reads aloud at the rate of one per second, and thus involve auditory attention. The testee has to repeat verbatim in the same sequence in the first section of the test, and in reversed order in the second section of the test. The first section has eight items with two digit series in each item. The second series has two practice examples that are not taken into account for scoring purposes, followed by seven items with two digit series in each item.

The test measures auditory short-term memory for numbers, but performance on this test is not inevitably an indication of memory for more complex information. The testee has to receive the information correctly, and recall, order and vocalize it correctly. Attention and concentration are also assessed.

The repetition of digit series in their usual order requires mainly mechanical memory, whereas the repetition of such a series in reversed order requires more complex abilities. In the latter section the testee has to store the information longer and convert the stimulus material before recalling it. Mental control is necessary here. It is assumed that memory, particularly mechanical memory, is one of the abilities of which a certain minimum is required at every level of intellectual functioning. The subtest is scored by awarding one raw score point for each correct trail. It is more useful to use the data in raw form than to convert them (Lezak, 1983).

Digits Forward measures efficiency of attention, or what is known as a " passive span of apprehension" (Hayslip and Kennely, 1980). Digit Span tends to be more vulnerable to left hemisphere involvement than to either right hemisphere or diffuse damage (Newcombe, 1969; Weinberg et al., 1972). Digits Backward is more of a memory test than Digits Forward. It involves mental double-tracking in that both the memory and the reversing operations must proceed simultaneously. Weinberg et al. (1972) suggests that the reversing operation depends upon internal visual scanning. The test is particularly sensitive to left hemisphere damage (Weinberg et al., 1972).

4.2.7 The Lahey Behaviour Checklist

It was found necessary to classify the subjects according to the maladaptive behaviours manifested by each. The Lahey Scale was used to assess the subjects. This method analyses empirically generated descriptions of malaptive behaviours, such as diagnostic descriptions used in child guidance clinics. Each item in the scale consists of a description of an aspect of maladaptive behaviour, with the full set of items, in theory , being representative of the entire range of maladaptive child behaviours. The resulting ratings are then factor analysed to isolate intercorrelated clusters of maladaptive behaviours. The scale includes items related to hyperactivity, conduct problems, learning disabilities,-and attention.

The scale was given to teachers, with written instructions, to mark all items typical of the child's behaviour that he /she engaged in more often than most other children. The teacher concerned rated the child and returned the ratings within a week. Certain questions to assess Tourette's Syndrome were included in the Checklist.

4.2.8   Deux Barrage (Barkley, 1990)

The Deux Barrage test consists of a sheet of paper on which a large number of symbols appear. This test measures the ability to concentrate fully, by circling two particular symbols. This test was devised to measure attentional and concentrational abilities in children (Barkley, 1990).

The instructions are to circle two particular symbols within a period of 180 and 360 seconds respectively. The number of correct symbols circled, indicates the child's ability to concentrate within the school environment. The test is scored by awarding one point for every item correctly circled, in 180 seconds and then in the second 180 seconds. The raw scores are used. The two scores are then compared. If the second score is significantly lower than the first score, then it is indicative of an attention difficulty. The symbols are constructed so as to have no meaning. However, they are intended to resemble figures and letters, in order to approximate a scholastic test. Barkley (1990) reported that he found this test particularly reliable and valid for the assessment of differences in concentrational abilities in children with learning difficulties.

Huysamen (1980) states that the validity of a test or measuring instument is determined by means of an investigation into the validity of a proposed interpretation or application of the test results. Therefore proof has to be given of the validity of the test for the purpose for which it is used. If a test is used for different purposes, the validity of the test has to be ascertained independently for each of the possible uses.
The aim of the tests used is to determine the subject's level of performance and to evaluate the relative strengths and weaknesses in certain important facets of neuropsychological development.

4.4   Procedure

The children in the group of Sudden Infant Death Syndrome siblings were used in a previous study (Chapman, 1991). They were obtained from The Cot Death Society and Compassionate Friends. The subjects diagnosed as suffering from Tourette's Syndrome were referred by various neurologists. These children were diagnosed according to the DSM-111-R classification for this syndrome. The control group were obtained from a local primary school, in a middle-class suburb. The subjects were described

126

as "average" by their teachers. They were selected as being representative of the general population, that is , not screened specifically for abscence of neurological deficits (Thoman, 1991, personal communication).

The groups of Attention Deficit Disorder and Attention Deficit Hyperactivity Disorder subjects were obtained from a local private remedial school. All had been diagnosed by neurologists or paediatricians, and other paramedical personnel, according to DSM-111-R classification. Due to the shortage of subjects with Tourette's Syndrome and siblings of Sudden Infant Death Syndrome the only exclusion criteria was if the subject had a below-average intelligence quotient, or manifested any form of pre-psychotic behaviour. The control group had to be matched to the Sudden Infant Death Syndrome siblings group as the Tourette's Syndrome group consisted entirely of boys whereas the Sudden Infant Death Syndrome sibling group consisted of both boys and girls.

The groups of subjects consisting of the Attention Deficit Disorder and Attention Deficit Hyperactivity Disorder were matched to the control and Sudden Infant Death Syndrome siblings groups for sex and age. However, the five groups are representative of the general population in all other ways. The parents were informed of the aim of the research study being undertaken and the form that the assessment would take explained. Parental consent was obtained for the children to be used in the study.

The children were assessed individually by a psychometrist, in a room at a local school, or in a suitable room at the child's home if the child lived too far from the particular school. The psychometrist was unaware whether the child belonged to the control, or one of the other four groups. It was emphasized that the child should view the various subtests as games and merely try to give of his/her best, and enjoy himself/herself. The various subtests administered were administered and scored according to the directions. All the subtests were administered by a psychometrist except for the Lahey Behaviour Checklist, which was completed by the teacher concerned. Tasks consisted of frequently used clinical procedures, and standardized tests (subtests from the Senior South African Individual Scale-Revised; SSAIS-R). The entire battery took 30 to 40 minutes to administer. After several minutes of familiarization, children were presented with the tasks as "games" and were encouraged to "do their best."

4.5   Research Design and Statistical Analysis

The research design comprised a comparison of the five groups on the relevant indices. The aim of the present study is to ascertain whether there is a possibility that, given the broad similarities in sub-

clinical brain damage leading to neuropsychological anomalies, Sudden Infant Death Syndrome infants, Sudden Infant Death Syndrome siblings, children diagnosed as suffering from Attention Deficit Hyperactivity Disorder or Attention Deficit Disorder and Tourette's Syndrome might manifest similar neuropsychological problems. The correlation between potentially revelant factors (e.g. sex, status, familial preference, pre- and perinatal complications, response to medication, neurological "soft" signs, developmental precursors and immaturity) (Taylor and Fletcher, 1983) appear to support a causal relationship between Attention Deficit Hyperactivity Disorder or Attention Deficit Disorder, Sudden Infant Death Syndrome siblings and Tourette's Syndrome.

CHAPTER FIVE

RESULTS

5.1   Introduction

A spectrum of attentional, perceptual-motor, visuo-practic, memory and coordination difficulties are found in children with diverse behavioural disorders (Harcherik, Carbonari et al, 1982). Because dysfunctions in basic psychological systems such as attention are hypothesized to underlie particular psychiatric disorders, children with a constellation of behavioural difficulties (impulsivity, inattention, poor concentration) have been characterised as suffering from "attention deficit disorders" (Harcherik, Carbonari et al, 1982).

These competences were assessed using a battery of tests with five groups of children, four with diagnosed disorders and a control group. The purpose was to compare the groups on multiple measures that have been used clinically to assess neuropsychological processes and to determine how the groups related to each other on these measures.

A double blind method of testing was used in the administration of the tests. Scores derived from systematic observation of a variety of cognitive, motor and social behaviours were encoded in a number of scales. The scores of the five groups; Sudden Infant Death Syndrome siblings, Tourette's Syndrome, Attention Deficit Hyperactivity Disorder, Attention Deficit Disorder and the control group, were compared on all the scales tested to determine the level of neurodevelopmental functioning and to determine whether significant differences between the five groups exist.

The specific hypothesis is:

There will be a significant difference between the neurodevelopmental functioning of a matched control group, siblings of Sudden Infant Death Syndrome infants, Attention Deficit Disorder, Attention Deficit Hyperactivity Disorder, and Tourette's Syndrome sufferers specifically in the areas of:

-       memory for verbal information - memory functioning,
-       memory for non-verbal information -memory functioning,
-       processing of non-verbal stimuli - information processing
-       visual-spatial arrangements - information processing
-       analytical ability, recognizing visual information - perception
-       global or gestalt thinking - information processing, and
-       social behaviour - performance

129

This chapter deals with the results and observations of the various subtests.

5.2   Difference statistics for the experimental and control groups for the combined scales.

5.2.1   Differences in vectors between the experimental and control groups for combined measures of the study

In order to determine if significant differences existed between the experimental and control groups on a combination of the measures used in the study, a multivariate analysis of variance was conducted.

A multivariate analysis of variance was used to determine the significance of differences between the experimental and control groups for a combination of measures used in this study. The multivariate analysis of variance showed a main effect due to the groups ($p < 0.001$: see Table 5.1).

TABLE 5.1

Multivariate analysis of variance: Differences between experimental and control groups on combined scores used in the study

Test Name	Value	Approx. F	Hypoth. DF	Error DF	p<
Pillais	0.80224	2.82234	16.00	180.00	$p < 0.001$
Hotellings	1.89694	4.80163	16.00	162.00	$p < 0.001$
Wilks	0.30815	3.78852	16.00	128.95	$p < 0.001$
Roys	0.62986				

Following this, a number of univariate analysis of variance was conducted to determine the degree of significance of differences between the experimental and control groups on individual variables.

5.3   Difference statistics for the experimental and control groups for scales measuring processing of information

An analysis of variance was conducted to determine the significance of differences between the groups on processing of information as assessed by the Trail Making Test (Trail A).

In order to establish the significance of differences between the groups on processing of information an analysis of variance was conducted. No significant main effect for the groups was found ($p > 0.05$; see Table 5.2).

TABLE 5.2

Analysis of variance: Significance of differences between the groups on processing of information as assessed by the trail making test (Trail A)

Variable	DF	Sum of Squares	Means Squares	F	P
Groups	4	672.08	168.02	1.0302	$p > 0.05$
Error Variance	45	7338.9	163.0867		

Because there was no significant main effect due to the groups, no post-hoc analysis was performed.

In order to establish the significance of differences between the groups on processing of information (Trail B) an analysis of variance was conducted. A significant main effect for the groups was found ($p < 0.05$; see Table 5.3).

TABLE 5.3

Analysis of variance: significance of differences between the groups on deficits in processing of information as assessed by the trail making test (Trail B)

An analysis of variance was conducted to determine the significance of differences between the groups on deficits of processing of information as assessed by the Trail Making test (Trail B).

Variable	DF	Sum of Squares	Means Squares	F	P
Groups	4	5346.7200	1336.6800	2.5059	$p < 0.05$
Error Variance	45	24004.0000	533.4222		

Because of the main effect due to the groups, a Scheffé post hoc analysis was conducted to determine significance of differences between the means.

A Scheffé post-hoc procedure was conducted to determine the significance of differences between individual cell means for visual scanning and tracking, as measured by Trail Making (B).

A significant difference was found between the group with Attention Deficit Hyperactivity Disorder and the control group ($p < 0.05$; see Table 5.4). Subjects with Attention Deficit Hyperactivity Disorder showed significantly more difficulty with visual scanning and tracking ($x = 76.8$; see Table 5.4) than the control group ($x = 47.5$; see Table 5.4).

131

A significant difference was found between the group of Tourette's Syndrome subjects and the control group (p < 0.05; see Table 5.4). Subjects with Tourette's Syndrome showed significantly more difficulty with visual scanning and tracking (x = 50.1)) than the control group (x = 47.5; see Table 5.4).

A significant difference was found between the group with Attention Deficit Disorder and the control group (p < 0.05; see Table 5.4). Subjects with Attention Deficit Disorder showed significantly more difficulty with visual scanning and tracking (x = 60.1; see Table 5.4) than the control group (x = 47.5; see Table 5.4).

A significant difference was found between the group of siblings of Sudden Infant Death Syndrome infants and the control group (p < 0.05; see Table 5.4). Siblings of Sudden Infant Death Syndrome infants showed significantly more difficulty with visual scanning and tracking (x = 50.1; see Table 5.4) than the control group (x = 47.5; see Table 5.4).

There were no other significant differences (see Table 5.4).

TABLE 5.4

Significance of differences between individual cell means

Group		Mean	B	C	D	E
ADHD	(A)	76.8	p < 0.05	p < 0.05	p < 0.05	p < 0.05
ADD	(B)	60.1		p < 0.05	p < 0.05	p < 0.05
SIDS	(C)	50.1				p < 0.05
TS	(D)	61.3				p < 0.05
Control	(E)	47.5				

5.4   Difference statistics for the experimental and control groups for scales measuring visual-motor integration

An analysis of variance was conducted to determine the significance of differences between the groups on visual-motor integration as assessed by the Digit Symbol sub test.

In order to establish the significance of differences between the groups on visual-motor integration an analysis of variance was conducted. No significant main effect for the groups was found (p > 0.04; see Table 5. 5).

TABLE 5.5

Analysis of variance: Significance of differences between the groups on visual-motor integration as assessed by the digit symbol subtest

Variable	DF	Sum of Squares	Means Squares	F	P
Groups	4	2036.48	509.12	2.6067	$p > 0.05$
Error Variance	45	8788.90	195.3089		

Because there was no significant main effect due to the groups, no post-hoc analysis was performed.

5.5 Differences statistics for the experimental and control groups on visual perception and logical reasoning

An analysis of variance was conducted to determine the significance of differences between the groups on logical reasoning and visual perception as assessed by the Pattern Completion test.

In order to establish the significance of differences between the groups on visual perception and logical reasoning an analysis of variance was conducted. A significant main effect for the groups was found ($p < 0.05$; see Table 5. 6).

Because of the main effect due to the groups, a Scheffé post hoc analysis was conducted to determine significance of the differences between the means.

A Scheffé post-hoc procedure was conducted to determine the significance of differences between individual cell means for logical reasoning and visual perception as measured by the Lahey Scale.

TABLE 5.6

Analysis of variance : Significance of differences between the groups on visual perception and logical reasoning as assessed by the pattern completion subtest

Variable	DF	Sum of Squares	Means Squares	F	P
Groups	4	181.92	45.48	2.5747	$p < 0.05$
Error Variance	45	794.9	17.6644		

A significant difference was found between the group with Attention Deficit Hyperactivity Disorder and

the control group (p < 0.05; see Table 5. 7). Subjects with Attention Deficit Hyperactivity Disorder showed significantly more difficulty with visual perception and logical reasoning (x = 8.1; see Table 5.7) than the control group (x = 13.7; see Table 5. 7).

A significant difference was found between the group with Tourette's Syndrome and the control group (p < 0.05; see Table 5.7). Subjects with Tourette's Syndrome showed significantly more difficulty with visual perception and logical reasoning (x = 9.9; see Table 5.7) than the control group (x = 13.7; see Table 5.7).

TABLE 5.7

Significance of differences between cell means for pattern completion

Group		Mean	B	C	D	E
ADHD	(A)	8.1	p < 0.05	p < 0.05		p < 0.05
ADD	(B)	11.7				p < 0.05
SIDS	(C)	11.9				
TS	(D)	9.9				p < 0.05
Control	(E)	13.7				

TABLE 5.8

Averages of scales by groups in the category information processing

	Trail A	Trail B	Digit Symbol	Pattern Completion
ADHD	31.0	76.8	32.3	8.1
TS	31.0	61.3	51.2	13.7
SIDS	39.0	50.1	45.8	11.9
ADD	37.9	60.1	39.8	9.9
CON	31.0	47.5	45.0	8.1

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+------------------------------------------------------------------+
|                          TABLE 5.9                               |
|  Analysis of variance : Significance of differences between the  |
|          groups on emotional                                     |
|     disturbance as assessed by the Lahey scale                   |
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Variable	DF	Sum of Squares	Means Squares	F	P
Groups	4	1221.320	305.33	24.4221	$p < 0.00001$
Error Variance	45	562.6	12.50		

5.6 Difference statistics for the experimental and control groups for scales measuring motor and social performance

5.6.1 Differences between the groups on emotional disturbance as assessed by the Lahey scale

An analysis of variance was conducted to determine the significance between the groups on emotional disturbance as assessed by the Lahey Scale.

In order to establish the significance of differences between the groups on emotional disturbance an analysis of variance was conducted. A significant main effect for the groups was found ($p < 0.05$, see Table 5. 10).

Because of the main effect due to the groups, a Scheffé post hoc analysis was conducted to determine significance of the differences between the means.

A Scheffé post-hoc procedure was conducted to determine the significance of differences between individual cell means for emotional disturbance as measured by the Lahey Scale.

A significant difference was found between the group with Attention Deficit Hyperactivity Disorder and the control group ($p < 0.05$; see Table 5. 10). Subjects with Attention Deficit Hyperactivity Disorder showed significantly more emotional disturbance ($x = 14.1$; see Table 5.10) than the control group ($x = 0.0$; see Table 5. 10).

A significant difference was found between the group with Tourette's Syndrome and the control group ($p < 0.05$; see Table 5. 10). Subjects with Tourette's Syndrome showed significantly more emotional disturbance ($x = 11.6$; see Table 5.10) than the control group ($x = 0.0$; see Table 5.10).

A significant difference was found between the group of Sudden Infant Death Syndrome siblings and

the control group (p < 0.05; see Table 5. 10). Siblings of Sudden Infant Death Syndrome victims showed significantly more emotional disturbance (x = 9.10; see table 5.10) than the control group (x = 0.0; see Table 5.9)

There were no other significant differences (see Table 5. 10).

TABLE 5.10

Significance of differences between individual cell means

Groups		Mean	B	C	D	E
SIDS	(A)	14.1	p < 0.05	p < 0.05	p < 0.05	p < 0.05 p <
ADD	(B)	5.4		p < 0.05	p < 0.05	0.05
TS	(C)	9.10			p < 0.05	p < 0.05
ADHD	(D)	11.60				p < 0.05
CON	(E)	0.0				

5.6.2   Differences between the groups on learning disabilities as assessed by the Lahey Scale

An analysis of variance was conducted to determine the significance of differences between the groups on learning disabilities as assessed by the Lahey Scale.

In order to establish the significance of differences between the groups on learning disabilities an analysis of variance was conducted. A significant main effect was found for the group was found (p < 0.00001; see Table 5. 11).

TABLE 5.11

Analysis of Variance : Significance of differences between the groups on learning disabilities as assessed by the Lahey Scale

Variable	DF	Sum of Squares	Means Squares	F	P
Groups	4	976.3200	244.0800	11.8857	p < 0.00001
Error Variance	45	924.100	20.5356		

Because of the main effect due to the group, a Scheffé post-hoc analysis was conducted to determine significance of differences between the means.

136

A Scheffé post-hoc procedure was conducted to determine the significance of differences between individual cell means for learning disabilities as measured by the Lahey Scale.

A significant difference was found between the group with Attention Deficit Hyperactivity Disorder and the control group ($p < 0.05$; see Table 5. 12). Attention Deficit Hyperactivity Disorder subjects showed significantly more learning disabilities ($x = 12.6$; see Table 5.12) than the control group ($x = 0.0$; see Table 5. 12).

A significant difference was found between the group of Sudden Infant Death Syndrome siblings and the control group ($p < 0.05$; see Table 5.12). Siblings of Sudden Infant Death Syndrome infants showed significantly more learning disabilities ($x = 11.0$; see Table 5. 12) than the control group ($x = 0.0$; see Table 5.12).

A significant difference was found between the group with Attention Deficit Disorder and the control group ($p < 0.05$; see Table 5. 12). Subjects with Attention Deficit Disorder showed significantly more learning disabilities ($x = 9.8$; see Table 5.12) than the control group ($x = 0.0$; see Table 5.12).

A significant difference was found between the group with Tourette's Syndrome and the control group ($p < 0.05$; see Table 5. 12). Subjects with Tourette's Syndrome showed significantly more learning disabilities ($x = 9.3$; see Table 5. 12) than the control group ($x = 0.0$; see Table 5. 12).

There were no other significant differences (see Table 5. 12).

TABLE 5.12

Significance of differences between individual cell means

Groups		Mean	B	C	D	E
ADHD	(A)	12.6	p < 0.05		p < 0.05	p < 0.05 p < 0.05
ADD	(B)	9.8				
SIDS	(C)	11.0				p < 0.05
TS	(D)	9.3				p < 0.05
CON	(E)	0.0				

5.6.3   Differences between the groups on attention (hyperactivity) as assessed by the Lahey Scale

An analysis of variance was conducted to determine the significance of differences between the groups

137

on Attention (Hyperactivity) as assessed by the Lahey Scale.

In order to establish the significance of differences between the groups on attention an analysis of variance was conducted. A significant main effect for the groups was found ($p < 0.05$; see Table 5. 13).

Variable	DF	Sum of Squares	Means Squares	F	P
Groups	4	1460.200	365.050	32.7366	$p > 0.05$
Error Variance	45	501.800	11.1511		$p < 0.00001$

TABLE 5.13

Analysis of Variance : Significance of differences between the groups on Attention (Hyperactivity) as assessed by the Lahey Scale

Because of the main effect due to the groups, a Scheffé post-hoc analysis was conducted to determine significance of differences between the means.

A Scheffé post-hoc procedure was conducted to determine the significance of differences between individual cell means for hyperactivity as measured by the Lahey Scale.

A significant difference was found between the group of Attention Deficit Hyperactivity Disorder subjects and the group of Attention Deficit Disorder and the control group ($p < 0.05$; see Table 5. 14). Subjects with Attention Deficit Hyperactivity Disorder showed significantly more hyperactivity ($x = 13.1$; see Table 5.14) than the group of Attention Deficit Disorder subjects and the control group ($x = 0.0$; see Table 5. 14).

A significant difference was found between the group with Tourette's Syndrome and the group of Attention Deficit Disorder subjects and the control group ($p < 0.05$; see Table 5. 14). Tourette's Syndrome subjects showed significantly more hyperactivity ($x = 10.0$; see Tabel 5.14) than the Attention Deficit Disorder subjects and the control group ($x = 0.0$; see Table 5. 14).

A significant difference was found between the group of Sudden Infant Death Syndrome victims siblings and the group of Attention Deficit Disorder subjects and the control group ($p < 0.05$; see Table 5. 14). Siblings of Sudden Infant Death Syndrome infants showed significantly more hyperactivity ($x = 8.9$; see Table 5.14) than the Attention Deficit Disorder subjects and the control group ($x = 0.0$; see Table 5. 14).

There were no other significant differences (see Table 5. 14).

TABLE 5.14						
Significance of differences between individual cell means						
Groups		Mean	B	C	D	E
ADHD	(A)	13.1	p < 0.05	p < 0.05	p < 0.05	p < 0.05 p <
ADD	(B)	0.0		p < 0.05	p < 0.05	0.05
SIDS	(C)	8.9				p < 0.05
TS	(D)	10.0				
CON	(E)	0.0				

5.6.4   Differences between the groups on conduct disorder as assessed by the Lahey Scale

An analysis of variance was conducted to determine the significance of differences between the groups on conduct disorder as assessed by the Lahey Scale.

In order to establish the significance of differences between the groups on conduct disorder an analysis of variance was conducted. A significant main effect for the groups was found ($p < 0.05$; see Table 5. 15).

TABLE 5.15					
Differences between the groups on Conduct Disorder as assessed by the Lahey Scale					
Variable	DF	Sum of Squares	Means Squares	F	P
Groups	4	938.480	234.620	8.7831	p > 0.05
Error Variance	45	1556.50	34.5889		p < 0.0002

Because of the main effect due to the groups, a Scheffé post-hoc analysis was conducted to determine significance of differences between the means.

A Scheffé post-hoc procedure was conducted to determine the significance of differences between individual cell means for conduct disorder as measured by the Lahey Scale.

A significant difference was found between the group with Tourette's Syndrome and the control group

(p < 0.05; see Table 5. 16). Subjects with Tourette's Syndrome showed significantly more conduct disorder (x = 4.3; see Table 5.16) than the control group (x = 0.0; see Table 5.16).

A significant difference was found between the Sudden Infant Death Syndrome siblings group and the control group (p < 0.05; see Table 5. 16). Siblings of Sudden Infant Death Syndrome infants showed significantly more conduct disorder (x = 6.4; see Table 5.16) than the control group (x = 0.0; see Table 5. 16).

A significant difference was found between the Attention Deficit Hyperactivity Disorder group and the control group (p < 0.05; see Table 5. 16). Subjects with Attention Deficit Hyperactivity Disorder showed significantly more conduct disorder (x = 5.8; see Table 5.16) than the control group (x = 0.0; see Table 5. 16).

A significant difference was found between the Attention Deficit Disorder group and the control group (p < 0.05; see Table 5. 16). Subjects with Attention Deficit Disorder showed significantly more conduct disorder (x = 4.3; see Table 5.16) than the control group (x = 0.0; see Table 5. 16).

There were no other significant differences (see Table 5. 16).

TABLE 5.16						
Significance of differences between individual cell means						
Groups		Mean	B	C	D	E
ADHD	(A)	5.80		.	p < 0.05	p < 0.05 p <
ADD	(B)	4.3			p < 0.05	0.05
SIDS	(C)	6.40			p < 0.05	p < 0.05
TS	(D)	13.40				p < 0.05
CON	(E)	0.0				

5.6.5   Differences between the groups on Tourette's Syndrome symptoms as assessed by the Lahey Scale

An analysis of variance was conducted to determine the significance of differences between the groups on Tourette's Syndrome symptoms as assessed by the Lahey Scale.

In order to establish the significance of differences between the groups on Tourette's Syndrome symptoms an analysis of variance was conducted. A significant main effect for the groups was found

(p < 0.05 ; see Table 5. 17).

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TABLE 5.17

Analysis of Variance : Significance of differences between the groups on Tourette's Syndrome symptoms as assessed by the Lahey Scale

Variable	DF	Sum of Squares	Means Squares	F	P
Groups	4	51.20	12.0	65.4545	p > 0.05
Error Variance	45	8.80	0.1956		p < 0.0002

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Because of the main effect of the groups a Scheffé post-hoc analysis was conducted to determine significance of the differences between the means.

A Scheffé post-hoc procedure was conducted to determine the significance of differences between individual cell means for Tourette's Syndrome symptoms as assessed by the Lahey Scale.

A significant difference was found between the group with Tourette's Syndrome and the other groups (p < 0.05; see Table 5. 18). Subjects with Tourette's Syndrome showed significantly more symptoms (x = 2.6; see Table 5.18) than the other groups (x = 0.00; see Table 5. 18).

There were no other significant differences (see Table 5. 18).

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TABLE 5.18

Significance of differences between individual cell means

Groups		Mean	B	C	D	E
SIDS	(A)	0.40			p < 0.05	
ADD	(B)	0.00			p < 0.05	
TS	(C)	2.60			p < 0.05	
ADHD	(D)	0.00				p < 0.05
CON	(E)	0.00				

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141

5.7 Differences statistics for the experimental and control groups for scales measuring laterality

5.7.1 Differences between the groups on laterality

An analysis of variance was conducted to determine the significance of differences between the groups on laterality.

In order to establish the significance of differences between the groups on laterality an analysis of variance was conducted. A significant main effect for the groups was found ($p < 0.05$; see Table 5. 19).

TABLE 5.19					
Analysis of Variance : Significance of differences between the groups on laterality					
Variable	DF	Sum of Squares	Means Squares	F	P
Groups	4	20.20	5.05	16.4674	$p < 0.0002$
Error Variance	45	13.8	0.3067		

Because of the main effect due to the groups, a Scheffé post-hoc analysis was conducted to determine significance of differences between the means.

A Scheffé post-hoc procedure was conducted to determine the significance of differences between individual cell means for laterality.

A significant difference was found between the group with Attention Deficit Hyperactivity Disorder and the control group ($p < 0.05$; see Table 5. 20). Subjects with Attention Deficit Hyperactivity Disorder showed significantly more laterality differences ($x = 1.6$; see Table 5.20) than the control group ($x = 0.0$; see Table 5. 20).

A significant difference was found between the Tourette's Syndrome group and the control group ($p < 0.05$; see Table 5. 20).

Tourette's Syndrome subjects showed significantly more laterality differences ($x = 1.5$; see Table 5.20) than the control group ($x = .0$; see Table 5. 20).

A significant difference was found between the Sudden Infant Death Syndrome siblings and the control group ($p < 0.05$; see Table 5. 20). The siblings of Sudden Infant Death Syndrome infants Group showed significantly more differences in laterality ($x = 1.4$; see Table 5.20) than the control group ($x = .0$; see Table 5. 20).

TABLE 5.20						
Significance of differences between individual cell means						
Groups		Mean	B	C	D	E
ADHD	(A)	1.60	p < 0.05	p < 0.05		P < 0.05
ADD	(B)	0.50				P < 0.05
SIDS	(C)	1.40				p < 0.05
TS	(D)	1.50				
CON	(E)	0.00				

TABLE 5.21					
Averages of scales by groups in the category Motor and Social Performance					
	Emotional Disturbance	LD	Hyperactivity	Conduct Disorder	TS
ADHD	14.1	12.6	13.1	5.80	0.00
TS	11.6	9.30	10.0	13.4	2.60
SIDS	9.10	11.0	8.90	6.40	0.40
ADD	5.40	9.80	0.00	4.30	0.00
CON	0.00	0.0	0.00	0.00	

5.8   Difference statistics for the experimental and control groups for scales measuring storage of information

5.8.1   Differences between the groups on auditory memory for meaningful verbal stimuli as assessed by the story memory subtest

An analysis of variance was conducted to determine the significance of differences between the groups on memory for meaningful verbal stimuli

In order to establish the significance of differences between the groups on auditory memory for meaningful verbal stimuli an analysis of variance was conducted. No significant main effect for the groups was found ($p > 0.05$; see Table 5.22).

Table 5.22

Analysis of Variance : Significance of differences between the groups auditory memory for verbal stimuli

Variable	DF	Sum of Squares	Means Squares	F	P
Groups	4	248.6800	62.1700	1.3444	$p > 0.05$
Error Variance	45	2081.0000	46.2444		

Because there was no significant main effect due to the groups, no post-hoc analysis was performed.

5.9   Differences between the groups on perceptual organization and visual memory as assessed the Ray Osterreith complex figure

An analysis of variance was conducted to determine the significance of differences between the groups on perceptual organization and visual memory as assessed by the Ray Osterreith Complex Figure.

In order to establish the significance of differences between the groups on perceptual organization and visual memory an analysis of variance was conducted. No significant main effect for the groups was found ($p > 0.05$; see Table 5. 23).

TABLE 5.23

Analysis of Variance : Significance of differences between the groups on perceptual organization and visual memory as assessed by the Ray Osterreith complex figure

Variable	DF	Sum of Squares	Means Squares	F	P
Groups	4	356.92	89.23	2.2656	$p > 0.05$
Error Variance	45	1772.3	39.3844		

Because there was no significant main effect due to the groups, no post-hoc analysis was performed.

144

5.9.1 Differences between the groups on visual memory as assessed by the Ray Osterreith complex figure

An analysis of variance was conducted to determine the significance of differences between the groups on visual memory as assessed by the Ray Osterrieth Complex Figure.

In order to establish the significance of differences between the groups on visual memory an analysis of variance was conducted. A significant main effect for the group was found ($p < 0.05$; see Table 5. 24).

TABLE 5.24
Analysis of Variance : Significance of differences between the groups on visual memory as assessed by the Ray Osterreith complex figure

Variable	DF	Sum of Squares	Means Squares	F	P
Groups	4	29.08	7.27	6.115	p < 0.05
Error Variance	45	53.50	1.1889		

Because of the main effect of the groups, a Scheffé post-hoc analysis was conducted to determine significance of differences between the means.

A Scheffé post-hoc procedure was conducted to determine the significance of differences between individual cell means for visual memory as measured by the Ray Osterrieth Complex Figure.

A significant difference was found between the group with Tourette's Syndrome and the control group ($p < 0.05$; see Table 5. 25). Subjects with Tourette's Syndrome showed significantly more difficulty with visual memory ($x = 1.4$; see Table 5.25) than the control group ($x = 3.5$; see Table 5. 25).

A significant difference was found between the group with Attention Deficit Hyperactivity Disorder ($p < 0.05$; see Table 5.25) and the control group. Attention Deficit Hyperactivity Disorder subjects showed significantly more difficulty with visual memory ($x = 1.5$; see Table 5.25) than the control group ($x = 3.5$; see Table 5. 25).

There were no other significant differences (see Table 5. 25).

TABLE 5.25

Significance of differences between individual cell means

Groups		Mean	B	C	D	E
ADHD	(A)	1.50	p < 0.05			
ADD	(B)	2.20				
SIDS	(C)	2.50				
TS	(D)	1.40				p < 0.05
CON	(E)	3.50				

TABLE 5.26

Averages of Scales by Groups in the Category Storage of Information

Groups	Auditory Memory	Perceptual Organizing	Visual Memory
		23.30	
ADHD	17.40	27.40	1.50
TS	19.30	26.10	1.40
SIDS	14.80	28.50	2.50
ADD	17.40	31.40	2.20
CON	21.50		3.50

5.10   Difference statistics for the experimental and control groups for scales measuring attention and perception of environmental cues

5.10.1   Differences between the groups on attention as assessed by the Deux Barrage subtest (Part 1)

An analysis of variance was conducted to determine the significance of differences between the groups on attention and concentration, as assessed by the Deux Barrage test.

In order to establish the significance of differences between the groups on attention and concentration an analysis of variance was conducted. No significant main effect for the groups was found (p < 0.05; see Table 5. 27).

TABLE 5.27

Analysis of Variance : Significance of differences between the groups on Attention and Concentration as assessed by the Deux Barrage subtest (Part 1)

Variable	DF	Sum of Squares	Means Squares	F	P
Groups	4	514.12	128.5300	0.7957	p > 0.05
Error Variance	45	7268.6	161.5244		

Because there was no significant main effect due to the groups, no post-hoc analysis was performed.

5.10.2 Differences between the groups on attention and concentration as assessed by the Deux Barrage subtest (Part 2)

An analysis of variance was conducted to determine the significance of differences between the groups on attention and concentration as assessed by the Deux Barrage subtest.

In order to establish the significance of differences between the groups an analysis of variance was conducted. A significant main effect for the groups was found (p < 0.05; see Table 5.28).

TABLE 5.28

Analysis of Variance : Significance of differences between the groups on Attention and Concentration as assessed by the Deux Barrage subtest (Part 2)

Variable	DF	Sum of Squares	Means Squares	F	P
Groups	4	2356.48	589.12	3.6773	p < 0.05
Error Variance	45	7209.30	160.2067		

Because of the main effect due to the groups, a Scheffé post-hoc analysis was conducted to determine significance of differences between the means.

A Scheffé post-hoc procedure was conducted to determine the significance of differences between individual cell means for the group.

A significant difference was found between the group with Attention Deficit Hyperactivity Disorder and the control group (p,0.05; see Table 5. 29). Subjects with Attention Deficit Hyperactivity Disorder showed significantly less ability to concentrate (x=23.8; see Table 5.29) than the control group (x=45.0; see Table 5. 29).

A significant difference was found between the group of Sudden Infant Death Syndrome siblings and the control group (p <0.05 ; see Table 5. 29). Siblings of Sudden Infant Death Syndrome victims showed significantly less ability to concentrate (x=30.6; see Table 5.29) than the control group (x=45.0; see Table 5.29).

A significant difference was found between the group with Tourette's Syndrome and the control group (p< 0.05; see Table 5.29). Subjects with Tourette's Syndrome showed significantly less ability to concentrate (x=33.1; see Table 5.29) than the control group (x=45,0; see Table 5.29).

A significant difference was found between the group with Attention Deficit Disorder and the control group (p< 0.05; See Table 5.29). Subjects with Attention Deficit Disorder showed significantly less ability to concentrate (x=34.4; see Table 5.29) than the control group (x=45,0; see Table 5. 29).

There were no other significant differences (see Table 5. 29)

TABLE 5.29

Significance of differences between individual cell means

Groups		Mean	B	C	D	E
ADHD	(A)	23.8	p < 0.05	p < 0.05	p < 0.05	p < 0.05
ADD	(B)	34.4		p < 0.05		p < 0.05
SIDS	(C)	30.6			p < 0.05	p < 0.05
TS	(D)	33.1				p < 0.05
CON	(E)	45.0				

5.11   Difference statistics for the experimental groups for scales measuring attention and mental control

5.11.1   Differences between the groups on attention and mental control as assessed by the digits forward and digit backward subtest

An analysis of variance was conducted to determine the significance of differences between the groups

on attention and mental control as assessed by the Digits Forward and Digits Backward subtest.

In order to establish the significance of differences between the groups on attention and mental control an analysis of variance was conducted. A significant main effect for the group was found ($p < 0.05$; see Table 5. 30).

TABLE 5.30

Analysis of Variance : Significance of differences between the groups on Attention and Mental Control As Assessed By The Digit Forward And Digit Backward Subtest

Variable	DF	Sum of Squares	Means Squares	F	P
Groups	4	195.08	48.77	4.0899	P < 0.05
Error Variance	45	536.6	11.9244		

Because of the main effect due to the groups, a Scheffé post-hoc analysis was conducted to determine significance of differences between the means.

A Scheffé post-hoc procedure was conducted to determine the significance of the differences between individual cell means for attention and mental control as assessed by Digits Forward and Digits Backward test.

A significant difference was found between the group with Attention Deficit Hyperactivity Disorder and the control group ($p < 0.05$; see Table 5. 31). Subjects with Attention Deficit Hyperactivity Disorder showed significantly more difficulty with attention and mental control ($x = 11.0$; see Table 5.31) than the control group ($x = 16.7$; see Table 5. 31).

A significant difference was found between the group with Attention Deficit Disorder and the control group ($p < 0.05$; see Table 5. 31). Attention Deficit Disorder subjects showed significantly more difficulty with attention and mental control ($x = 11.8$; see Table 5.31) than the control group ($x = 16.7$; see Table 5.31).

A significant difference was found between the group of Sudden Infant Death Syndrome siblings ($p < 0.05$; see Table 5.31) and the control group. Sudden Infant Death Syndrome siblings showed more difficulty with attention and mental control ($x = 12.5$; see Table 5.31) than the control group ($x = 16.7$; see Table 5.31).

A significant difference was found between the group with Tourette's Syndrome and the control group ($p < 0.05$; see Table 5.31).

Subjects with Tourette's Syndrome showed significantly more difficulty with attention and mental control ($x = 13.4$; see Table 5.31) than the control group ($x = 16.7$; see Table 5.31).

There were no other significant differences (see Table 5.31).

TABLE 5.31							
Significance of differences between individual cell means							
Groups		Mean	B	C	D	E
ADHD	(A)	11.0		$p < 0.05$	$p < 0.05$	$p < 0.05$
ADD	(B)	11.8			$p < 0.05$	$p < 0.05$
SIDS	(C)	12.5				$p < 0.05$
TS	(D)	13.4				$p < 0.05$
CON	(E)	16.7				

TABLE 5.32			
AVERAGES OF SCALES BY GROUPS IN THE CATEGORY ATTENTION AND PERCEPTION OF ENVIRONMENTAL CUES			
	Deux Barrage 1	Deux Barrage 2	Digits F & B
ADHD	36.2	23.8	11.0
TS	40.3	33.1	13.4
SIDS	40.8	30.6	12.5
ADD	42.4	34.4	11.8
CON	46.1	45.0	16.7

CHAPTER 6

CONCLUSION

6.1   INTRODUCTION

In Attention Deficit Hyperactivity Disorder, the essential deficit would appear to be one of difficulty in the central arousal system. This is often followed by deficiencies in terms of the perceptual motor bases of learning of symbolically encoded material as well as the processing thereof. It would appear from the literature that the problem in terms of perception as far as the developmental learning disabilities are concerned are most noticeable on measures of visual-perceptual, visual-spatial and psychomotor abilities. It appears that they have some central processing deficiency, that is, they have marked difficulty in organizing, integrating, and/or synthesizing information as a result of some type of neurological dysfunction. Difficulty with short-term memory for both verbal and non-verbal stimuli was also noted. Social adjustment, and related emotional growth and development were also problematic areas.

Numerous studies using various psychological tests have established the presence of information processing deficits among Attention Deficit Disorder children despite normal performance of many standard psychometric tests   (Rosenthal & Allen, 1978). The issue of developmental change is particularly relevent for understanding the nature of Attention Deficit Disorder since it is essentially defined as a disorder of maturation; that is, the cognitive and behavioural abilities of the Attention Deficit Disorder child are not seen as deviant, but rather as developmentally inappropriate for the child's chronological and mental age. The Attention Deficit Disorder children in this study revealed a relatively distinct and circumscribed pattern of cognitive deficits. They were impaired on tasks requiring sustained attention, cognitive flexibility and regulation of goal-directed activity through the use of environmental feed-back. Particularly notable were the Attention Deficit Disorder children's perseverativeness and apparent decreased responsivity to reinforcement in guiding their problem solving behaviours. These results suggest that Attention Deficit Disorder children may have an underlying dysfunction of the inhibitory forebrain system controlling attentional processes in response to situational demands.

Previous research has been inconclusive regarding the cognitive profiles of children with Tourette's Syndrome. Psychological test findings in Tourette's Syndrome children, utilizing neuropsychological tests have provided consistent evidence for cognitive deficits similar to those found in children with known brain damage (Incagnoli & Kane, 1981). These studies demonstrated consistent impairment of circumscribed functions. An interesting cluster of deficits considered to represent a dysfunction of

151

nonconstructional visuopractic abilities was found. These included visual-motor coordination, perceptual organization, and short-term memory. Lezak (1976) has noted that deficits in visuographic functions may occur independently of a construction dyspraxia; this would appear to be the case for the subjects in this investigation.

While such deficits are typically considered cortical in nature, it is not known whether these impairments are the result of neurophysiological irregularity. Some of the inconsistency in the cognitive functioning of Tourette's Syndrome children may be due to the presence of attentional and hyperactivity problems in a substantial number of Tourette's Syndrome patients. Relative weaknesses in Socialization skills, that is, interpersonal relationships, coping skills , were noted and point to a level of social functioning that fell considerably below chronological age expectations. This suggests that many Tourette's Syndrome children show delay in social adaptation relative to other areas of adaptive functioning. This group also evidenced a significant amount of parental difficulty in consistently handling the consequences of noncompliant behaviour.

It would appear that in the instance of Sudden Infant Death Syndrome, the basic problem would manifest itself in an arousal deficiency, and more specifically, in the breathing reflex, where essentially the breathing reflex is inhibited by a lack of arousal in the Central Nervous System. It was postulated and to quite a fair degree substantiated by the work of Chapman (1991) who indicated that due to lowered arousal and therefore less effective breathing reflex responsivity, especially at night, a slow apnea would ensue. It appears that the data obtained in that study supported the hypothesis that siblings of Sudden Infant Death Syndrome infants possibly exhibit neurodevelopmental dysfunction. Furthermore, they manifest many similarities with children who suffer from Attention Deficit Hyperactivity Disorder, both on a cognitive, behavioural and social adjustment level.

It would appear that a neurological maturation defect would play a central role in the development and maintenance of the four Neuropsychological Syndromes of childhood discussed in the study. In essence, a neurodevelopmental lag would manifest in either a localized maturational lag resulting in differential levels of maturation and subsequent poor neuronal integration or that tha maturational lag would be more central in terms of the processing of information coming from the otherwise intact cortex. However, maturational lag can also manifest in a lag in the development of either appropriate levels of arousal, or inappropriate projection of those fibres to the cortex, and therefore inappropriate levels of arousal at cortical level. Therefore, the arousal mechanism as well as the information processing mechanism associated with maturational lag would have its focus on poor mylenization of the appropriate neurons in the appropriate areas. The poor mylenization could be the result of defects in one or more of the areas associated with normal maturation. Herein an immunological deficit related

to a superabundance of testosterone in the developing fetus (Geschwind et al, 1983).

Luria's theory of neurological development is based upon both functional and physiological changes that occur with normal maturation. He described five stages extending from birth through adolescence (the time neurological development is considered complete). Different stages of development are related to the functional maturation of various cortical areas. Luria envisioned the brain divided into three principal units responsible for: 1. arousal and attention; 2. sensory input integration and coding, and 3. behavioural planning and execution. The areas within each of these units develop in a hierarchical sequence and have specialized functions. However, overt behaviour is the result of the hierarchical organization and the interdependence among these different areas of the brain. The pattern of interacting areas responsible for a particular behaviour is called a functional system. Each area of the brain participates in numerous functional systems. When a functional system is interrupted by brain injury, then learning problems may occur. The extent and type of the learning disorder depends on the time of injury during the developmental sequence, the significance of the functional systems disturbed, and availibity of alternate functional systems. Luria (1980) acknowledged that basic perceptual and motor functions were, for the most part, well localized.

It would appear that a central arousal deficit in Attention Deficit Hyperactivity Disorder is largely responsible for the deficits noted. Less of a central arousal deficit in Attention Deficit Disorder is involved, or it is possible that in Attention Deficit Disorder, the central arousal is boosted or bolstered by means of perceptual hyperactivity rather than motor activity. Tourette's Syndrome and siblings of Sudden Infant Death Syndrome siblings, who generally show a high level of hyperactivity, would be affected in the same manner as the sufferers of Attention Deficit Hyperactivity Disorder.

The difficulties noted appear to lie on a continuum with relative weighting towards one or other side, some on the perceptual, some on the processing side. It could be expected that a fair degree of overlap exists between these conditions and that they might be various manifestations of differential levels of maturity. However, it was noted that the groups vary on the composite neuropsychological index.

6.2   Conclusion

In order to differentiate between indices of neuropsychological learning, emotional and social dysfunction, between the groups of Sudden Infant Death Syndrome victim siblings, Tourette's Syndrome, Attention Deficit Hyperactivity Disorder, and Attention Deficit Disorder children, it would be important to first ascertain the effects of the differences between these groups in terms of neuropsychological functioning. In terms of the neuropsychological model postulated previously, a

specific focus was placed on neuropsychological variables in perception, information processing, memory functioning, and performance in terms of learning disabilities and social behaviour.

In terms of perception, it was found that there were significant differences between siblings of Sudden Infant Death Syndrome victims, children with Attention Deficit Disorder, Attention Deficit Hyperactivity Disorder and the control group. Of note here, is that the siblings of Sudden Infant Death infants appear to show difficulty with perception of patterns as well as logical and sequential reasoning surrounding visual patterns, whereas Attention Deficit Hyperactivity Disorder, and Attention Deficit Disorder could be differentiated between verbal learning difficulties, therefore having difficulty with sequentialing processes associated with the left hemisphere or non-verbal learning disabilities associated with simultaneous processing of information, for which the right hemisphere is specialized. It could be postulated that the groups of Attention Deficit Disorder and Attention Deficit Hyperactiviy Disorder children contain mixed verbal and non-verbal learning disabilities, therefore showing that Sudden Infant Death Syndrome infant siblings would manifest greater difficulty with sequential and logical reasoning, or processing of visual information. In terms of Hoppenbrouwers and Hodgman (1982) who proposed a core deficit of mild hypoxia sustained during pre- and post-natal life, for which the majority of infants successfully compensates, but over a period of time may render the infant more vulnerable to other risk conditions.

These influences include conditions in utero, mild perinatal insults, premature delivery,, and post-natal environment conditions. Research has shown that siblings of Sudden Infant Death Syndrome infants manifest many of the symptoms shown by the affected infant, but to a lesser degree. Partial hypoxia left much less permanent damage. Nyka (1976a) found that only early hypoxia caused brainstem damage in humans. This suggests that the onset, duration and relative intensity of hypoxia are relevent variables. Nyka related his finding to the rate of cell division and tha resulting large energy demand of maturing cells in the brainstem. This would infer that the siblings suffered from hypoxia when the higher order functioning areas responsible for logical reasoning and sequential learning, in the left hemisphere were at there most vulnerable, that is, during mylenization.

It appears that a subset of Attention Deficit Disorder and Attention Deficit Hyperactivity Disorder children that have non-verbal learning disabilities do not manifest difficulty with logical and sequential reasoning. Because of the pervasive, generalized effect of hypoxia, siblings of Sudden Infant Death syndrome infants have generalized neuropsychological dysfunction which would by definition, impact more severely on higher order reasoning, higher order conceptualization and information processing, such as logical sequential reasoning. It would appear that the difficulty or neuropsychological dysfunctioning would apply more to higher order conceptualization and information processing than on

154

actual perceptual difficulties.

Furthermore, children with Tourette's Syndrome showed more difficulty with visual perception and logical sequential reasoning of visual stimuli than children with Attention Deficit Disorder. Deficits in visuopractice performance has been documented by a number of authors and appear to be quite consistent (Thompson et al, 1979; Incagnoli and Kane, 1981; Harcherik et al, 1982). It therefore appears that Tourette's Syndrome sufferer's disabilities are more pervasive and generalized, perhaps even partly substantiating Comings and Comings' hypothesis, therefore indicating greater disability than Attention Deficit Disorder sufferers. The problems obviously have a complex origin and are the result of interactions among overall intelligence, neuropsychological strengths and weaknesses, and motivation, as well as psychological, social, and interpersonal factors. Whereas children with Attention Deficit Disorder do not have such severe difficulty with disinhibition as Attention Deficit Hyperactivity Disorder children, manifesting only an attention deficit, their deficit is attentional in nature and not central processing.

However, this was not substantiated in the Trails B Test, a test more specifically designed for information processing. Attention Deficit Hyperactivity Disorder children manifested the most severe dysfunction and showed more deficit than Sudden Infant Death Syndrome siblings, Attention Deficit Disorder, Tourette's Syndrome children and the control group. If a comparison be drawn between the higher order conceptualization and sequential reasoning required in the Pattern Completion and Trails B tests, it could be theorized that Trails B is a simpler test involving simultaneous processing sequentially of data, and also visual acuity and the simultaneous perception of the entire stimulus configuration. This would appear to substantiate the fact that higher order sequential processing is more deficient in Sudden Infant Death Syndrome infant siblings because of the pervasive neuropsychological deficit of the hypoxic damage, while this was not as evident when the stimuli was singular and concrete necessitating simultaneous processing as well as sequential processing on a lower level than on the Pattern Completion Test. Therefore, the overactivity in terms of motor and perceptual overactivity would be a far more distracting event in terms of the simultaneous processing of a visual stimulus.

When attention to visual stimuli was analysed, very few differences were found. It was found that Sudden Infant Death Syndrome infants siblings had greater difficulty than the control group. It is possible that the Deux Barrage test does not measure concentration and attention sufficiently, that the task is too short and repetitive, so that the child's attention is not sustained. No significant difference in attention and concentration was found, except that all the groups showed significant differences from that of the control group. It therefore appears that a variety of pediatric neuropsychological disorders would be associated with attention deficits, because it is a disinhibitory condition, and numerous

psychiatric conditions can present as attention difficulties (Rostain, 1991). However, when memory was assessed, it was found that Sudden Infant Death Syndrome infant siblings and Attention Deficit Disorder children experienced more visual memory deficits than the control group. The same groups also experienced more difficulty with memory for verbal stimuli. It is to be expected that Tourette's Syndrome and Attention Deficit Hyperactivity Disorder children would show greater memory deficits than the control group, because of their obvious neuropsychological deficits.

It therefore appears that the pervasive neuropsychological deficits experienced by siblings of Sudden Infant Death Syndrome infants would render insignificant by comparison the other conditions, partly because of the concentration difficulties experienced, as well as an apparent difficulty in recall of visual and verbal stimuli. It would appear that while the neuropsychologically impaired children would mainifest greater difficulty with concentration and attention when compared to the control group, no significant difference was found between the various groups. However, it was found that siblings of Sudden   Infant Death Syndrome infants appeared to be the most severely impaired neuropsychologically, as both their visual and auditory memory are severely impaired. Their complex reasoning is impaired in terms of logical sequencing and sequential information processing, while their concrete information processing and simultaneous management of information processing would be less impaired. However, when the external manifestations of neuropsychological impairment is analysed, it was found that siblings of Sudden Infant Death Syndrome infants were more learning disabled by their teachers than any of the other groups. They were also found to be more hyperactive. However, their teachers did not perceive them to be more emotionally disturbed, or more conduct disordered. It is postulated that the neuropsychological impairment manifested by siblings of Sudden Infant Death Syndrome infants is pervasive and not merely disinhibitory in nature, and although overactive, they do not appear to manifest with emotional disturbance.

The research results showed that Tourette's Syndrome children appear to manifest more emotional disturbance than Attention Deficit Disorder and the control group, they are also perceived to be more hyperactive, although they are not perceived to be more conduct disordered. The conclusion that can be drawn from the above research, taking into consideration that there were certain difficulties with the research, that is, a limited number of subjects, a limited number of tests used, the possibility that tests tapped certain problems in certain populations more severely than in others. The conclusion would appear to be that the subgroups of Attention Deficit Hyperactivity Disorder and Attention Deficit Disorder are separate groups,and that Tourette's Syndrome groups separately from the other two. Furthermore, it would appear that the group that one would predict to be the most neuropsychologically impaired, namely siblings of Sudden Infant Death Syndrome infants, because they are near-Sudden Infant Death Syndrome infants, would manifest the greatest neuropsychological impairment.

156

Attention Deficit Disorder children appeared to be the least impaired of the groups. However, the children in this study revealed a relatively distinct and circumscribed pattern of cognitive/behavioural deficits. Attention Deficit Disorder children did not differ on most measures of mental processing, but were impaired relative to the controls on tasks requiring sustained attention, cognitive flexibility and regulation of goal directed behaviour, behaviours thought to be mediated, in part, by the frontal lobes. The results suggest that Attention Deficit Disorder children may, in fact, have an underlying dysfunction of the inhibitory forebrain system controlling attentional processes in response to situational demands, thus substantiating Chelune et al's (1986) findings. They did not show a significant discrepancy between their sequential and simultaneuos processing skills. This negative result may be interpreted as failing to support the frontal lobe hypothesis of Attention Deficit Disorder. Alternatively, it may be argued that the tests used do not adequately assess sequential and simultaneous processing. Frontal lobe dysfunction is also related to disinhibition and disorders of social conduct in both children and adults and have been conceptualized as manifestations of frontal lobe involvement. Attention Deficit Disorder children scored significantly higher on conduct disorder than three of the other groups, corroborating Chelune et al's (1986) findings. In summary, the results of the present study provide partial support for the frontal lobe dysfunction theory of Attention Deficit Disorder. Children diagnosed Attention Deficit Disorder were found to have a relatively circumscribed pattern of neuropsychological deficits on tests presumed to measure frontal lobe functioning.

Attention Deficit Hyperactivity Disorder children were found to have higher scores on both emotional disturbance and conduct disorder, and a higher score than three of the other groups on hyperactivity, thus substantiating several authors research (Frick, Lahey et al, 1991; Lahey, Schaughency et al, 1987). This group also manifested a relatively circumscribed pattern of deficits on tests presumed to measure frontal lobe inhibitory control. The Attention Deficit Hyperactivity group were more severely affected neuropsychologically than the group with Attention Deficit Disorder, presumably because of their disinhibition deficits. Hyperactivity is often among the behavioural sequelea associated with frontal lobe lesions (Hecaen, 1989). The results of the study suggest frontal lobe involvement in cognitive processes, exacerbated by hyperactivity.

Therefore, the groups are significantly different. Each group showing different manifestations. Siblings of Sudden Infant Death Syndrome infants manifesting more pervasive and all-embracing disabilities, but not manifesting with emotional disturbance. Attention Deficit Hyperactivity Disorder children manifest difficulty with attention and concentration, and information processing, particularly simultaneous processing of information, and problem solving, resulting in hyperactivity, emotional problems, conduct disorder, and social disinhibition. However, their central processing does not appear to be effected. Siblings of Sudden Infant Death Syndrome are more severely impaired neuropsychologically. They are

157

perceived to be more hyperactive, and be more learning disabled. However, they do not appear to manifest with emotional and conduct disorders. It is possible that, because of the pervasive nature of their neuropsychological deficit, they could manifest blunted affect and therefore very little emotive interaction that could be construed as conduct disorder. Apneic/anoxia associated with Sudden Infant Death Syndrome would destroy mid-brain as well as higher-level cortical function, resulting in flatness of affect. However, the results of this study do indicate some frontal lobe involvement.

It would appear that whereas these groups differ and manifest differential problems, Sudden Infant Death Syndrome is a pervasive neuropsychological condition, not related to other pediatric conditions, and should not be treated as such. Tourette's Syndrome, Attention Deficit Disorder and Attention Deficit Hyperactivity Disorder definitely differ from each other on all scores, with Tourette's Syndrome appearing not to be the most neuropsychologically deficited or behaviourally impeded in any of the areas, as has previously been theorized. However, the deficits noted constitute a relevant and interesting cluster of deficits. The commonality of function among these various tasks is considered to represent a dysfunction of nonconstructional visuopractic abilities. Several researchers (Sweet, Bruun, Shapiro, & Shapiro, 1974; Sweet, Solomon, et al, 1973; Woodrow, 1974) consider the etiology of Tourette's Syndrome to involve a neurophysiological disorder of the central nervous system, probably of the basal ganglia. The role of the basal ganglia in regulating motor functions is widely known. Pribram (1977) has stressed the importance of the basal ganglia for sensory input in primates, especially in relationship to visual processing.

The pattern of neuropsychological deficits in the Tourette's Syndrome sample confirms the results of previous investigations. Tourette's Syndrome children appear to have deficits on tests that require visuospatial visuomotor skills. Specifically, the deficit appears to be restricted to nonverbal tasks requiring spatial or motor components as well. The visuomotor deficits that occurred tended to be bilateral. A focal structural lesion would seem an unlikely explanation for this pattern of deficits. However, the fact that the deficits tended to be nonverbal and visuospatial in nature might implicate the right cerebral hemisphere. The presence of bilateral visuomotor and sensory perceptual deficits would not be completely incompatible with this as previous research has suggested that bilateral tactile perceptual deficits are found after right hemisphere lesions, whereas only contralateral deficits are associated with left hemisphere lesions (Boll, 1974).

If the underlying abnormality in Tourette's syndrome is neurochemical, it is possible that the right hemisphere is more susceptible to disruption than the left hemisphere. It has been suggested that the hemispheres have different patterns of neural organization in that the right hemisphere is more diffusely organized (Gur, et al, 1980). This more diffuse organization might increase the vulnerability of the right

hemisphere to a neurochemical abnormality. Evidence that the right hemisphere may be more susceptible to generalized systemic changes can be found in studies that suggest that the right hemisphere ages more quickly than the left (Goldstein & Sherry, 1981). A greater vulnerability of the right hemisphere could account for this pattern of neuropsychological deficits which seems to implicate the right hemisphere in a syndrome in which the likely etiology is a neurochemical abnormality.

The circumscribed, though highly consistent, deficits found in Tourette's Syndrome subjects were visuographic in nature. While such deficits are typically considered cortical in nature, it is not known whether these impairments are secondary results of neurophysiological irregularity of the basal ganglia or whether they are manifestations of a primary lesion of the cerebral cortex. It is also not known whether the etiology of these deficits involves a neurochemical or a focal structural lesion. The deficits found suggests a pattern of neuropsychological deficit which is consistent with previous reports of cognitive difficulties in Tourette's Syndrome. These children tend to exhibit fairly frequent deficits on certain types of tasks. The bilateral motor and sensory-perceptual difficulties would lend support to a bilateral disturbance. The circumscribed nature of the deficits which have been observed argues against a specific or focal lesion as the source of the neuropsychological deficits. from the data accumulated it appears that a diffuse subcortical disturbance, possibly neurochemical, which for some unexplained reason, produces behavioural deficits which seem to implicate the right cerebral hemisphere more than the left.

Furthermore, relative weaknesses in socialization skills, that is, emotional disturbance, and coping skills, pointed to a level of social functioning that fell considerably below chronological age expectations. Although these data do not establish whether or not this weakness in socialization is secondary to the stigmatizing effects of Tourette's Syndrome symptoms, they do suggest that many Tourette's Syndrome children show a delay in social adaptation. It is therefore possible that Tourette's Syndrome children form a small subset of pediatric neuropsychological disorders. This would conform to the DSM-111-R view of the dysfunction, and not with Comings and Comings view and would conform to the Yale School's view as postulated to be narrowly defined condition. Despite the consistency of results, the need for cross-validation on a larger sample is clear. Future investigations should also be designed so as to determine whether such noted deficits are due primarily to sensory or to motor dysfunction, or their integration. It is possible that this type of information would have direct bearing on remediation strategies for educational and other forms of intervention with Tourette's Syndrome children.

The neuropsychological model postulated is that:

*   Siblings of Sudden Infant Death Syndrome infants manifest more severe and diverse neuropsychological deficits than the other groups assessed because of the pervasive nature of the neuropsychological damage;

*   the various groups manifested a circumscribed pattern of deficits;

*   the various groups differed from each other;

*   attention deficit is manifested by all children suffering from neuropsychological syndromes, to varying degrees.

In summary, this study has found that siblings of Sudden Infant Death Syndrome infants are more neuropsychologically impaired than the other groups, exhibiting more severe deficits with visual and auditory memory and problems with logical sequencing and sequential information processing. Children with Tourette's Syndrome's most severe impairment was in the area of visuopractic abilities, and socialization skills. Attention Deficit Hyperactivity Disorder children were more impaired than Attention Deficit Disorder children, particularly regarding socialization skills. Attention Deficit Disorder children were the least impaired of the groups, manifesting mainly attentional difficulties. however, the sample size precludes the generalization to the population at large. This study has provided support for the viability of such an assumption, and needs to be investigated more thoroughly.

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163

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171

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172

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