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Autism: the aetiology, management, and treatment modalities with the dental perspective in mind

A dissertation submitted to the University of Hong Kong in partial fulfilment of the requirement for the Post-graduate Diploma in Dental Surgery in Paediatric Dentistry

By

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2001

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This book was a gift from

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ABSTRACT

This dissertation is a literature review of investigations from the late 1970's to the most recent articles on autism, with a special emphasis of its application on dental care. Autism has been known as a developmental disorder of the brain. Most autistic children have a repetitive tendency and deficient communication skills. Their level of intelligence ranges from total mental impairment to supreme giftedness. The prevalence of autism is reported at 2-5 per 10,000 people. Early investigation in the 1970's perceived autism as a psychological illness from family problems. But researchers in the 1980's believed that autistic children suffered from some inborn neuronal structural deficiencies. Most recent research in the late 1990's reveals that autism is an inherited genetic disorder as a result of germ cell mutations, chromosomal aberrations and gene-locus fragility.

Physicians have concentrated on the use of medication in the management of autism with limited success. Most investigators believe their use will make autistic patients amenable to behavioural treatment. Behavioural interventions remain as the mainstream of autism management and various strategies have been advocated to modify the maladaptive behaviours of autistic children.

Dental investigation has shown that autistic children and adolescents have low incidence of dental caries. That may be attributed to their special preference of
non-sweetened food. These patients generally have a high incidence of gingivitis because of their low oral hygiene status. Some autistic children exhibit atypical oral habits in that they are susceptible to some self-inflicted gingival trauma. Autistic children and adolescents are uncooperative in the dental office and dentists often require the use of various pharmacological agents and behavioural modification in order to complete necessary treatment. Among all the available management methods, the use of general anaesthesia remains the ideal method even with its associated risks and cost.
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Chapter 1  The clinical features and diagnosis of autism

Autistic children have been known to have impairment in their social interaction, and repetition in their actions and behaviour. They also have many other clinically significant features. Because of the behavioural nature of autistic disorder and the lack of any specific diagnostic test, diagnosis is generally based on information derived from parental reports and clinical observation (Stone et al., 1994). The core clinical features of autism include impairment in social interaction, deficits in both verbal and non-verbal communication, and restricted, repetitive, and stereotyped patterns of behaviour, interests and activities (Tsai, 1999). The clinical features of autism will be presented in the following sections: social deficits, deficiency in communication, language, and symbol use, restricted and odd range of activities and interests, atypical intellectual capacity, and impairment in imitation, pointing and gesture, eye gaze, and repetitive activities.

1.1 SOCIAL DEFICITS

The most notable feature of autism is the qualitative abnormal character of autistic children’s reciprocal social interaction (Rapin, 1991). He described several general features of autistic children in terms of their socialisation defects. First, as infants, autistic children may resist cuddling. Even as toddlers and pre-schoolers, they may walk past people or bump into them as though they did not see them. Second, they have gaze avoidance, unaware of other person’s feelings, and
inadequate ability to interpret tone of voice and facial expression. Third, autistic children also do not know how to make friends, and engage other children in play and seem to enjoy social isolation. They are rigid, and do not learn social greetings; however, some are inappropriately affectionate and will kiss a perfect stranger and some have exclusive attachment to their mothers.

The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV Text version) lists the following features on the impairment in the reciprocal social interaction. The diagnostic criteria of DSM-R for autistic disorder are also summarised in table 1-1.

(1) Marked impairment in the use of multiple non-verbal behaviour (e.g. eye-to-eye gaze, facial expression, body posture, and gestures) to regulate social interaction and communication.

(2) Failure to develop peer relationships appropriate to developmental level.

(3) Little or no interest in establishing friendships in younger individuals.

(4) Older individuals may have an interest in friendship but lack understanding of the conventions of social interaction.

(5) Lack of seeking to share enjoyment, interests, or achievements with other people.

(6) Lack of social or emotional capacity may be present (e.g. not actively participating in simple social play or games, preferring solitary activities, or involving others in activities only as tools or mechanical aids.

(7) They may be oblivious to other children (including siblings), and they may have no concept of the needs of the others or not notice another person's distress.

(American Psychiatric Association, 2000)
Wing et al. (1997) categorised autistic children into three groups on the basis of their social skills: aloof children who are essentially passive, children who are more reachable but tend to gravitate away from social interaction unless actively engaged, and active-but-odd children who can initiate interactions but do

Table 1-1. Summary of DSM-III-R Diagnostic Criteria of Autistic Disorder (Stone et al. 1994).

A. Qualitative impairment in reciprocal social interaction
   1. Marked lack of awareness of the existence or feelings of others
   2. No or abnormal seeking of comfort at times of distress
   3. No or impaired imitation
   4. No or abnormal social play
   5. Gross impairment in ability to make peer friendships

B. Qualitative impairment in communication and imagination
   1. No mode of communication
   2. Markedly abnormal nonverbal communication
   3. Absence of imaginative activity
   4. Marked abnormalities in the production of speech
   5. Marked abnormalities in the form of content of speech
   6. Marked impairment in the ability to initiate or sustain a conversation, despite adequate speech

C. Markedly restricted repertoire or activities and interests
   1. Stereotyped body movements
   2. Persistent preoccupation with parts of objects or attachment to unusual objects
   3. Marked distress over changes in trivial aspects of environment
   4. Unreasonable insistence on following routines in precise detail
   5. Markedly restricted range of interests
go in awkward, stilted, and inappropriate ways. All these social impairments can be detected as early as in children who are very young, and they cause dysfunction of social interactions at early developmental levels. Such information on social skills may be particularly relevant to the identification of autism in pre-school children who have significant cognitive impairment (Vig and Jedrysek, 1999). To sum up, autistic children generally have significant and pervasive deficits in the acquisition of adaptive social skills (Rodigue et al., 1991)

1.2 DEFICITS IN COMMUNICATION AND SYMBOL USE

Failure to acquire language at the expected age (Rapin, 1991), a total lack of the development of spoken language (American Psychiatric Association [APA], 2000) and the lack of pretend play are some of the most frequently presenting complaints of pre-school autistic children. In fact, developmental language disorder (dysphasia) is quite common among autistic children. Some are word-deaf, and others acquire language late and speak unintelligibly in short sentences with incorrect structures. Delayed echolalia is another common communication feature of autism in which autistic children speak a fluent unintelligible jargon that contains bits and pieces of memorised television commercials or separated phrases. The DSM-IV case book (1994) illustrates this with a case of a 3½ years old autistic boy Richard that “at age 3, he could understand simple practical instruction...his speech consisted of echoing some words, and phrases he had heard in the past, with the original speakers accent and intonation.”
The impairment of communication in autistic children is marked and sustained and there may be delay in a total lack of the development of spoken language (APA, 2000). When speech does develop, the pitch, intonation, rate, rhythm or stress may be abnormal. Grammatical structures are often immature and include stereotyped and repetitive use of language. A disturbance in the social use of language is often evidenced by an inability to integrate words with gestures or understand speech or non-literal aspects of speech such as irony or implied meaning. In fact, these children speak to themselves, and have little need for a conversational partner (Rapin, 1991). Verbal autistic children do not know how to participate in conversation, maintain topics, take turns, look at their conversational partners, or interpret tone of voice, facial expressions and body language. They may speak in a monotone, too loudly, or softly or in a singsong fashion. Autistic children, thus, have deficits in their communication and understanding skills.

Non-communicative vocalisation may be observed in children who function at early developmental levels (Vig and Jedrysek, 1999). Freeman et al. (1981) stated that although both groups repeated sounds, preschoolers with autism and IQs below 70 did so less frequently than preschoolers with mental impairment. Diagnostic criteria involving atypical language may not be applicable to preschool children because these children, whether they have autism or not, may have little or no language (Stone et al., 1991). Hence, other characteristics other than non-communicative vocalisation such as repetition of sounds, and symbolic plays are used to diagnose autism in younger children.
The lack of symbolic play, similarly, is another one of the criteria used to diagnose autism in young individuals. The definition of symbolic play, or pretend play is that objects are used as if they have other properties or identity and which is normally present by 12-15 months old children (Baron-Cohen et al., 1992). It is listed as one of the diagnostic criteria to diagnose autism in the DSM-IV (Vig and Jedrysek, 1999). Several investigators have studied symbolic play in children with developmental problems. Baron-Cohen et al.(1992, 1996) identified deficits in pretend play as a key factor associated with a subsequent diagnosis of autism in two studies of 18 month-olds at genetic risk for autism. This deficit seems to be highly specific but there is not a general absence of play. For example, children with autism do show functional play, which is the use of toys as they are intended to be used, and sensormotor play, which is the exploration of the physical properties of objects with no regard to their functions like banging, waving, sucking and throwing (Baron-Cohen, 1987). An example of pretend play is that a child makes appropriate noises while pushing a toy car along, or pretends to drive it into a garage to fill up with petrol or holding dolls as if there were real babies and brushing their hair and putting them in bed (Wing and Gould, 1977). Autistic children, nevertheless, seem unable to perform these types of activities. Sigman et al. (1987) attributed those autistic children’s lack of symbolic play to have an inability to abstract concepts or store the abstractions symbolically; therefore, the lack of representational play may be important for identifying autistic spectrum disorders in pre-schoolers.
1.3 RESTRICTED AND UNUSUAL RANGE OF ACTIVITIES AND INTERESTS

Autistic children regularly display repetitive movements (stereotypies or mannerism). The flapping of hands, twirling, humming, running around in circles, rocking, head banging, twisting their fingers and twiddling locks of hair sometimes to the point of baldness (Rapin, 1991) are some examples of such movements. They may vehemently resist change in routines or the environment and have unusual tolerance for monotony. As an illustration, a young child may intently study letters, numbers, or a phone book rather than play and some children engage in verbal stereotypies such as singing a particular song or repeating a single joke again and again. Autistic children are often characterised by their strange, and repetitive behaviour.

Children with significant cognitive impairment are reported to have fewer restricted, repetitive or stereotyped activities than those who have better cognitive function and children who are older (Vig and Jedrysek, 1999). They stated that the very young and cognitively lower functioning children may manipulate objects nonspecifically like touching, dropping, sliding across surfaces, and spinning-lining up objects. They may not show interest in any details of objects or may lack sufficient cognitive development to recognise patterns or similarities among objects or events. Thompson and Berkson (1988) studied children ranging from 1 to 16 years old who had severe developmental delay. They described that stereotyped behaviour with objects increased with chronological age and with higher developmental ages and IQs; therefore, the level of repetition and
stereotypic behaviour are positively correlated to the cognitive functioning of the autistic children.

Delong (1994) did evaluated behaviour between children with autistic spectrum disorder and manic-depression. He studied 40 autistic children and their behavioural characteristics. The relative proportions of each characteristic are listed in table 1-2. According to table 1-2, characteristics that are shared by more than 60 of the autistic children studies are poor social relating, poor play skills, shuts people out, gaze aversion, delayed speech development, poor communicative speech, telegraphic speech, delayed echolalia, difficulty with open-ended language tasks, repetitiveness, difficulty making transitions, stereotyopies, effective extremes (explosive, willful), attention deficits, obsessions and verbal reasoning difficulty.

Even though hand mannerisms like hand flapping, finger wiggling and finger flicking are common features among autistic children, the presence of hand stereotypies should be used cautiously for differential diagnosis of autism (Vig and Jedrysek, 1999). Lord (1995) compared children with autism and mental impairment at mean ages of 2 and 3 years. He noted over 87% of autistic children and 38% of mentally impaired children had manual mannerisms. However, at a 3 year retest, the 87% of the autistic group continued to have the hand stereotypes but only 8% of the mentally impaired group still had the problem. Schultz and Berkson (1998) explain that
Table 1-2. Behavioural symptoms in children with autistic spectrum disorder.

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<tr>
<th>Symptoms</th>
<th>Children with ASD(N)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor social relating</td>
<td>35</td>
<td>87.5</td>
</tr>
<tr>
<td>Poor play skills</td>
<td>34</td>
<td>85</td>
</tr>
<tr>
<td>Shuts people out</td>
<td>32</td>
<td>80</td>
</tr>
<tr>
<td>Gaze aversion</td>
<td>03</td>
<td>75</td>
</tr>
<tr>
<td>Delayed speech development</td>
<td>24</td>
<td>60</td>
</tr>
<tr>
<td>Poor communicative speech</td>
<td>34</td>
<td>85</td>
</tr>
<tr>
<td>Telegraphic speech</td>
<td>13</td>
<td>32.5</td>
</tr>
<tr>
<td>Delayed echolalia</td>
<td>20</td>
<td>50</td>
</tr>
<tr>
<td>Pronounce reversal</td>
<td>11</td>
<td>27.5</td>
</tr>
<tr>
<td>Difficulty with open-ended language tasks</td>
<td>31</td>
<td>77.5</td>
</tr>
<tr>
<td>Regression of language and social response</td>
<td>08</td>
<td>20</td>
</tr>
<tr>
<td>Preservation repetitiveness</td>
<td>34</td>
<td>85</td>
</tr>
<tr>
<td>Difficulty in making transitions</td>
<td>27</td>
<td>67.5</td>
</tr>
<tr>
<td>Stereotypies</td>
<td>33</td>
<td>82.5</td>
</tr>
<tr>
<td>Poor co-ordination, clumsy</td>
<td>16</td>
<td>40</td>
</tr>
<tr>
<td>Stiff, rigid posture</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>Poor fine-motor co-ordination</td>
<td>15</td>
<td>37.5</td>
</tr>
<tr>
<td>Affective extremes</td>
<td>31</td>
<td>77.5</td>
</tr>
<tr>
<td>Willful, explosive</td>
<td>27</td>
<td>67.5</td>
</tr>
<tr>
<td>Fearful</td>
<td>22</td>
<td>55</td>
</tr>
<tr>
<td>Cycles of behaviours</td>
<td>23</td>
<td>57.5</td>
</tr>
<tr>
<td>Distractibility, attention deficits</td>
<td>32</td>
<td>80</td>
</tr>
<tr>
<td>Special interests, fixations</td>
<td>28</td>
<td>70</td>
</tr>
<tr>
<td>Obsessions</td>
<td>4</td>
<td>17.5</td>
</tr>
<tr>
<td>Numbers, letters</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>Lists (presidents, kings, etc.)</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Game show, television</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>Music, songs, song titles</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Mechanical (cars, hinges, electronics, etc.)</td>
<td>17</td>
<td>42.5</td>
</tr>
<tr>
<td>Other (water colours, spinning objects, etc.)</td>
<td>22</td>
<td>55</td>
</tr>
<tr>
<td>Imaginary characters, fantasy</td>
<td>9</td>
<td>22.5</td>
</tr>
<tr>
<td>Hyperlexia</td>
<td>12</td>
<td>30</td>
</tr>
<tr>
<td>Ecopressi</td>
<td>8</td>
<td>20</td>
</tr>
<tr>
<td>Good memory for vocabulary, facts</td>
<td>14</td>
<td>35</td>
</tr>
<tr>
<td>Problems with verbal reasoning</td>
<td>28</td>
<td>70</td>
</tr>
</tbody>
</table>

(Adapted from Delong, 1994)
hand stereotypies are more common in the lower than the higher functioning group in the age range from 7 to 13 years old. Results of studies of hand mannerisms suggest that this diagnostic feature is found in both children with autism and with mental impairment without autism. Due to this overlap of features, we should be careful to use this as a sole feature to diagnose autism (Vig and Jedrysek, 1999).

1.4 ATYPICAL INTELLIGENCE- THE IDIOTS-SAVANTS

Most investigators agree that autistic children have a wide range of intellectual capacity. Even though the mean IQ of the autistic population is low, at least 30% of autistic individuals have an IQ above 70 (DSM-IV). The majority of individuals with autistic disorders have IQs in the moderate to severe range of mental impairment (Rapin, 1999). Typically, autistic children tend to have much better non-verbal (visual-spatial) than auditory verbal skills. Consequently, the IQ score is particularly likely to be misleading in persons with language disorders, inasmuch many subtests of IQ are verbal, their solution may be enhanced by a verbal strategy (Rapin, 1991).

Many autistic children have low intelligence to the mentally impaired level while there are some who are exceptionally talented. Autistic persons with such a superb intelligence are often referred to as "idiot-savants" (Rapin, 1991). They are characterised by having specific high-level performance and outstanding talents despite of some degree of mental impairment (O'Connor and Hermelin, 1991).
The nature of talents in idiot-savants has been investigated by several researchers. Autistic savants were shown to have exceptional capabilities in the areas of musical performance (Hermelin et al., 1987), graphic art (O'Connor & Hermelin, 1987), calendar calculation (O'Connor & Hermelin, 1984), and various forms of mnemonomism such as knowledge of bus routes (O'Connor & Hermelin, 1989), and train timetables.

Hermelin et al. (1987) performed a study of the musical inventiveness of five idiots-savants. Their personal background history is described in table 1-3. In their study, idiots-savants who were musically gifted were noted to be far superior to normal controls in both of their musical inventiveness and their competence level. Two of these subjects were autistic and three were blind. Despite their severely restricted interaction with the environment, it may be possible that they found the production of musical sounds and the invention of musical sequences as highly rewarding activities. Therefore, these activities like music allowed them a degree of control over a subject matter which they otherwise lacked.

A similar talent in another area which is well documented of the idiots-savants, despite of their generally low cognitive level, are their outstanding drawing and painting capabilities. O'Connor and Hermelin (1987) performed a test in which five idiots-savants whose artistic output was judged to be at art school entrance standard were compared for performance and verbal IQ with control subjects who had no special artistic talent. They
Table 1-3. Case history of some autistic children (Hermelin et al. 1987)

Subject I

The subject is 19 years old. He attended schools for the mentally handicapped between ages five and seventeen. He has a diagnosis of autism and now lives in a sheltered community for autistic youngsters. He is in an almost total absence of spontaneous speech, and does not look at other people and displays some bizarre and obsessive behaviour patterns. His abilities are very limited, and he could not lead an independent life. His musical ability was first noted in school when he was eight, he spontaneously took the music teacher's place at the piano, playing all that he had previously heard. There was no piano in his home and he has developed his own fingering technique. He spends two mornings per week making music, which includes choir practice, bell-ringing, and a piano lesson. His favourite instrument is piano, but he can also play the recorder and the guitar.

He continually listens to the music on the radio and will play anything he has listened to after about three hearings. He has acquired a large classical repertoire, including Beethoven and Mozart sonatas. He also plays popular songs and hymns. In a previous study this subject showed that his musical memory was based on an appreciation of conventional musical structure and did not extend to atonal music.

Subject II

This man is now aged 58. He was totally blind from birth. At the age of five he was deemed unsuitable for education and was placed in an institution for mentally handicapped children. At the age of 16 years he was transferred to another institution where he has remained ever since. There are no reports about musical ability in the case history, except that he was noted as a child to be able to remember a very large number of songs. He spends about three hours per week on music, including choir singing, playing in a band and a music therapy session. He sings and he is a percussion player.

He listens a great deal to the radio and his talent for composing songs was noticed seven years ago. Since then he has invented a large number of songs for which he supplies his own words. This is one of his texts:

'Let us thank our Father for his loudly day
For the frosty meadows where was love to play
Thank you for the daisies glistening in the dew
Thank you for the sunshine and skies so blue
In the living treetops birds are very small
Children let us thank our Father for them all.'

Subject III

This 18-year-old boy was diagnosed as autistic and attends a school for autistic children. When he was 13 his verbal mental age was reported to have been at a two-year-old level, and he talked only in one-word sentences. He played obsessively with bricks, and also compulsively played the same few tunes on the piano, which he had begun to play spontaneously at the age of eight. He is reported to have always had a remarkable musical memory and he has had music therapy and music lessons for several years. At first he got very upset when a piece of music was played in a different key or varied in any way from the original. Now he has learned to sight-read and has greatly enlarged his repertoire. He is not willing to learn new pieces and will also play together with others.

He has an individual piano lesson of half and hour per week and spends another half-hour at a group music lesson. Apart from the piano, he plays the guitar, and spends a good deal of time playing these instruments.
Figure 1-1. Drawings of idiots savants: retarded male; performance IQ 55 (O'Connor and Hermelin, 1987).
Fig 1-2. Drawings of idiots savants: autistic female; performance IQ 55 (O’Connor and Hermelin, 1987)
Fig. 1-3. Drawings of idiots savants; autistic female; performance IQ 36 (O’Connor and Hermelin, 1987).
Fig. 1-4. Drawings of idiots savants: retarded male with autistic features; performance IQ 62 (O’Connor and Hermelin, 1987).
were all asked to draw a man, and a test of picture completion. In all tests, the autistic savants showed clearly superior drawing ability than the IQ matched controls. Such results indicated that these savants have an IQ-independent talent and a superior imagememory as a form of a “picture lexicon”. Some of the sample drawings are presented in figure 1-1 to 1- 4.

Autistic children, especially those who are classified as idiot-savants, are characterised to have a tendency to repetitive behaviours, and preoccupation with a restricted area of interest. O’Connor and Hermelin (1991) performed a questionnaire survey on 40 subjects with 20 autistic savants, 20 autistic mentally impaired non-savants and autistic non-savants.. They found the following results. First, when autistic savants were compared with autistic controls, savants were found to show significantly more interest in one particular object and the obsessional ordering of possessions. Second, the non-savant autistic children were distinguished from the savants by showing less repetitive behavioural and obsessional behaviour. Third, all autistic subjects showed less anger at the disturbance of routines than the mentally impaired. Fourth, autistic non-savant group showed less neat ordering and less tendency to mention or particular topic than did the autistic savants. They concluded that idiots-savants were overall more strongly inclined to repetitive behaviours and more preoccupied with one topic than were the controls.

1.5 Imitation, Pointing and Gazin- Joint-Attention Behaviour
Many investigators have reported that autistic children have early impairment in some joint-attention behaviours like imitation, finger pointing, and eye gazing. Jarold et al. (1993) suggested that impaired imitation was an early manifestation of a deficit in forming and co-ordinating self-other representations. Such deficit was thought to lead to impaired emotion later in life. Sigman et al. (1986) indicated that joint-attention behaviour was absent and rare in autistic children. Joint-attention behaviour includes pointing, showing, and gaze monitoring, and it is defined as attempts to monitor or direct the attention of another person to an object or event (Baron-Cohen et al., 1992). Since both pretend play and joint-attention behaviour are normally present in simple forms by 15 months in children, their absence at the routine 18-month screening could be clear and specific indicators of autism or related pervasive developmental disorders. Osterling and Dawson (1994) suggested that pointing and showing objects differed for children with autism from those with normal development. Mars et al. (1998) found that showing objects and pointing with gaze had differences in normal children from autistic children when they reviewed home videotapes of social events at the time the children were 12 to 30 month old. Autistic children rarely point to an object, hold an object up for a caregiver to see, bring an object to the caregiver, or use indicating gestures (Vig and Jedrysek, 1999). Furthermore, some autistic children were found to be more apt to use another person's body as a tool like holding an adult by the wrist and directing the adult's hand towards a desired object (Mundy et al., 1994).

Atypical eye gaze is another joint-attention behaviour that most autistic children exhibit. The DSM-IV list inadequate use of eye gaze to regulate social
interaction as one of the diagnostic criteria for autism (APA, 2000). Children with autism could be differentiated from normal children by whether or not they looked at other people (Osterling and Dawson, 1994). Mars et al., (1998), similarly, stated that looking at people and alternating gaze could differentiate children with autism from normal development. Autistic children tend to look at their own objects only without looking at other people's eyes. For instance, when an adult teased the children by offering an object and playfully withdrawing it, all of the normal children would look at the adult's eyes to determine his/her intention. However, few of the children with autism would do so (Vig and Jerdrysek, 1999).

Baron-Cohen et al. (1997) suggested that children with autism were relatively insensitive to a speaker's gaze direction as an index of the speaker's intention to refer. This result is consistent with the findings that children with autism are relatively blind to the mentalistic significant of the eyes. They described that the "speaker's direction of gaze" was important for children to narrow down the possible search space of likely objects. As an illustration, if a speaker says "Dog!" while looking at a dog, upon hearing this word for the first time the child infers that because the speaker's gaze is currently directed toward the hairy thing on the rug, that is what is being picked out rather than the armchair next to it or the lamp above it. They referred to this as the Speaker's Direction of Gaze (SDG) strategy.

There is an alternative strategy called the Listener's Direction of Gaze (LDG) strategy. This is an assumption that a novel word uttered by a speaker refers to the object that the listener is currently looking at. Such strategy, if used
indiscriminately would often lead to children’s making mapping errors in which a world is mistakenly linked to an incorrect object. Another class of language error commonly noted in autistic children is when they use their own private words to refer to objects rather than the socially conventional usage. Baron-Cohen and co-workers (1997) noted that they knew a child with autism who called a toy truck a “sausage”. Such a saying would never be produced by the normal 18 month-old child. The authors explained the child had presumably failed to check the mother’s direction of gaze and so he learned the wrong association.

Baron-Cohen and co-workers (1997), furthermore, expanded the concept of the SDG and LDG strategies into the language delay feature of autistic children. Without the SDG strategy, which may well be a result of an executive dysfunction (Ozonoff, 1995), the child language learner would be forced to use the alternative LDG strategy. The latter strategy would lead to mapping errors such that the child mislabelled the wrong object because the speaker’s focus of attention was different from that of the child. They stated that the first feature of autistic language would be the production of same worlds being used in unconventional ways. In addition, such a lack of the SDG strategy would slow down the autistic child’s rate of language development. Without the normal ability to infer the language code through the speaker’s direction of gaze, the autistic child would mislabel objects and ultimately lead to many false starts, conflicting information, and confusion.

Not understanding the conventional way of communication, the child with autism would lose the motivation for vocabulary acquisition due to the mapping error. Baron-Cohen et al. in the same paper proposed a hypothesis:

if a child first hears the word ‘computer’ when Daddy is sitting at this desk at home typing away, and the child is
looking at his or her toy bricks on the floor, the LDG strategy would lead to the mapping ['computer' = bricks]. If the same child next hears the word 'computer' when Mommy is in her office and the child is looking at the goldfish tank, the child would search his or her lexical memory, retrieve the item 'computer', which would produce the interpretation 'bricks'; but then not finding any bricks at his or her current perceptual field. The child would delete the mapping ['computer' = bricks], and substitute this with ['computer' = goldfish] (page 55).

The child presumably would turn to more predictable ways of the environment such as some repetitive and stereotyped behaviour after several of these mismapping errors. In short, Baron-Cohen et al. concluded that such a lack of the Speaker's Direction of Gaze (SDG) in young children with autism is part of a joint-attention deficit and also a deeper deficit in showing a focus of attention both verbally and non-verbally.

1.6 CONCLUSIONS

Autism is a developmental disorder of the brain. The manifestation is largely behavioural and it seriously affects the child’s normal development of sociability and language communication. Most affected children develop a repertoire of activities and interests. Their level of intelligence ranges from total mental impairment to superior giftedness. Their cognitive skills are highly uneven with better non-verbal than verbal skills. All autistic children have developmental language disorder. Their verbal expression may range from total lack of language to echolalia while their comprehension of language is invariably impaired.
Chapter 2 The epidemiology of autism

2.1 INTRODUCTION

The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, American Psychiatric Association, 1994) categorises the autistic spectrum disorders under the broad category of Pervasive Developmental Disorders (PDD). Autism has been known as a rare disorder. The epidemiology of autism is a study of the prevalence and incidence of its occurrence, and its related medical disorders and other information such as sex ratio, and age differences. These data are important in designing educational programs and medical treatment for children with autism. The rate of autism is often reported at 2-5 in 10,000 people (Combe, 1996). But Wing (1996) reported that autism spectrum disorders might be as prevalent as in 1 in 100. And so, there is a possibility that autism is not as rare as it was once thought.

2.2 THE PREVALENCE OF AUTISM- IS ITS PREVALENCE INCREASING?

According to a review article by Gillberg and Wing (1999), they stated there were eight studies published in the 1990’s and they showed higher autism rates than previous studies. The results of seven of these studies are summarized in table 2-1. All of these non-US studies in the 1990’s showed higher autism rates than previous studies in the 1970’s and 1980’s. The mean prevalence during this period was 9.07 per 10,000 (Gillberg and Wing, 1999). In comparison, the two U.S. studies shows significant lower rates of autism; their prevalence rates are 3.3/10,000 and 3.6/10,000.

<table>
<thead>
<tr>
<th>Studies (1990-1997)</th>
<th>Place</th>
<th>Population rate (n/10,000)</th>
<th>N</th>
<th>M:F(M:F)</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gillberg et al. (1991)</td>
<td>Sweden</td>
<td>9.5 (7.4-11.9)</td>
<td>74</td>
<td>55:19 (2.89)</td>
<td>78,100</td>
</tr>
<tr>
<td>Deb &amp; Prasad (1994)</td>
<td>Scotland</td>
<td>9.0 (7.2-11.0)</td>
<td>91</td>
<td>66:22 (2)</td>
<td>101,800</td>
</tr>
<tr>
<td>Baron-Cohen et al. (1996)</td>
<td>UK</td>
<td>6.3</td>
<td>10</td>
<td>?</td>
<td>16,000</td>
</tr>
<tr>
<td>Nordin &amp; Gillberg (1996)</td>
<td>Sweden</td>
<td>9.0 (5.1-14.9)</td>
<td>15</td>
<td>10:5 (2)</td>
<td>16,600</td>
</tr>
<tr>
<td>Webb et al. (1996)</td>
<td>UK</td>
<td>9.2 (6.3-12.9)</td>
<td>33</td>
<td>29:4 (7.25)</td>
<td>35,900</td>
</tr>
<tr>
<td>Honda et al. (1996)</td>
<td>Japan</td>
<td>21.1 (16.2-21.1)</td>
<td>18</td>
<td>13:59 (2.6)</td>
<td>8,500</td>
</tr>
<tr>
<td>Arvidsson et al. (1997)</td>
<td>Sweden</td>
<td>31.0 (11.6-68.4)</td>
<td>6</td>
<td>5:1 (5)</td>
<td>1,900</td>
</tr>
</tbody>
</table>

autistics= 247 Total:258,800

US studies

<table>
<thead>
<tr>
<th>Studies</th>
<th>Place</th>
<th>Population rate (n/10,000)</th>
<th>N</th>
<th>M:F(M:F)</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burd et al. (1987)</td>
<td>Dakota, US</td>
<td>3.3 (2.5-4.2)</td>
<td>59</td>
<td>43:16</td>
<td>181,000</td>
</tr>
<tr>
<td>Ritvo et al. (1989)</td>
<td>Utah, US</td>
<td>3.4 (2.9-4.1)</td>
<td>125</td>
<td>95:30</td>
<td>365,000</td>
</tr>
<tr>
<td>total:</td>
<td></td>
<td></td>
<td>184</td>
<td></td>
<td>546,000</td>
</tr>
</tbody>
</table>

The total number of people surveyed in this pooled analysis was 258,800 for the non-US studies and 546,000 for the US studies. The prevalence of autism in the non-US group was 9.54/10,000 while the US group was 3.37/10,000. There seemed to be a trend towards increasing numbers of autism from the two studies which were conducted in the US (Gillberg and Wing, 1999). America stood out to have atypically low findings. This could be a function of the greater difficulty of coverage in epidemiological studies in the US and real geographical differences in the prevalence of autism. A few studies, like the one by Honda et al., reported the prevalence rate of autism to be 16.0/10,000 to 21.1/10,000 in a town of Japan. Such high rates were commonly found in studies which were performed in very small populations and the findings must therefore be interpreted with particular caution. Another study by Kadesjo and Gillberg (1995) was conducted in a very small population in Sweden. Likewise, their report showed that the autism prevalence had an even higher value of 1/1000. Gillberg and Wing described all of the smaller scale studies with high rates cannot be immediately dismissed as a likely reflection of chance findings. Another possibility was that the rise was due to greater awareness of autism.
Another reason, furthermore, of such an increase in the prevalence was the effect of immigration. Gillberg et al. (1991) performed an epidemiological study in Goteberg, Sweden. They found that almost all of the parents of autistic children had been born in non-neighbouring countries of Sweden. They suggested three reasons for such rises in prevalence and incidence. First, the rises were due to the possibility of genetic disorders exclusive to the native region of the parents. Second, prenatal, and perinatal brain damages were likely to be more common in less developed countries even though the brain was quite resistant to the physical insult from the birth process (Mason-Brothers et al., 1987). Some of these insults were maternal viral infections in pregnancy and metabolic disorder triggered by environmental factors in the new country. Third, interuterine viral infections (e.g. rubella) might be more common among children born to mothers who did not have viral antibodies and contacted infections after immigration. In summary, Gillberg et al. found that the rate of autism in Goteberg, Sweden was higher than previously thought and the rate was in the range of 1/1000 rather than 1/2000 to 1/5000 (Gillberg et al., 1991; Gillberg and Wing, 1999). These unusual values were attributed to some possible medical consequences of immigration.

2.3 PRENATAL, PERINATAL, AND NEONATAL FACTORS- THE UTAH STUDY

Families with single cases of autism were shown to have greater occurrences of bleeding, flu like symptoms, and medication during the mothers’ pregnancies (Mason-Brothers et al., 1987). The same team performed a similar epidemiological survey in 241 autistics in Utah, USA in 1989. The perinatal factors studied are summarized in table 2-2. The state of Utah is an ideal location for this type of investigations since the
population size is very small (1.6 million), geographically stable, and highly cooperative with medical researchers. The most important aspect is that they have kept extensive genealogical records for religious purposes.

<table>
<thead>
<tr>
<th>Prenatal factors</th>
<th>Utah study</th>
<th>Finegan &amp; Quarrington</th>
<th>Devkin &amp; MacMahon</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>A</td>
<td>A S</td>
<td>S</td>
</tr>
<tr>
<td>Bleeding</td>
<td>4/225(18%)</td>
<td>9/61(15%)</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>17/225(8%)</td>
<td>11/60(18%)</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>7/220(3%)</td>
<td>2/59(3%)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>21/221(10%)</td>
<td>7/59(12%)</td>
<td>-</td>
</tr>
<tr>
<td>Edema</td>
<td>109/221(49%)</td>
<td>32/55(58%)</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>52/230(24%)</td>
<td>7/59(12%)</td>
<td>0</td>
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<td>13</td>
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<td></td>
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<td>9</td>
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<td>3</td>
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<td>4</td>
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<td>37</td>
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</table>

Table 2-2 contains the data from the Utah study and two other published surveys by Finegan & Quarrington (1979) and Dyekin & MacMahon (1989) for comparison. Toxemia was the only factor that occurred significantly more often in non-autistic than autistics in the Utah data. Severe nausea during pregnancy, however, occurred twice as often among mothers in the autistic group (24%) than those in the non-autistic group (12%). Then tendency of bleeding during pregnancy, and the increase uses of medication were not significant in the Utah study. Mason-Brothers (1989), similarly, collected data in terms of anaesthesia, methods of delivery, types of labour, the during of labour, placenta excretion, cord problems, rupture rates, and excessive bleeding of the mothers’ pregnancies with autistic children and other pregnancies with normal siblings. They found that no significant differences between the two types of pregnancies.
2.4 NEONATAL FACTORS

Investigators of autism used to agree lower birth weight was the only feature to distinguish autistic males from their non-autistic male siblings. These findings were very different from those of Finegan and Quarrington (1979). They found that the cause of autism could be multifactorial; there were more incidences of low birth weights, haemolytic disease, high serum bilirubin level and respiratory distress. Mason-Brothers et al. were unable to associate any of the pathologic prenatal, perinatal and neonatal events with autism. They concluded that the foetal brain was remarkable resistant and resilient to insults and so few maternal risk factors could be identified for autism in offspring. In addition, they assumed that if pathologic factors led to autism, they must be stable, operate in combination and/or be present at the time of conception or very early in neural tube or foetal brain development. Hence, genetic factors may well be the causative agents (see Chapter 4).
### Table 2-3 Neonatal factors in autism

<table>
<thead>
<tr>
<th>Prenatal factor</th>
<th>Utah Population</th>
<th>Finegan &amp; Quarrington</th>
<th>Deykin &amp; MacMahon</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Autistic /222</td>
<td>Nonaustic /62 %</td>
<td></td>
</tr>
<tr>
<td>Birth weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2270 g</td>
<td>12</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>2270-2724g</td>
<td>10</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>2724-3178g</td>
<td>64</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>3178-3632g</td>
<td>83</td>
<td>37</td>
<td>26</td>
</tr>
<tr>
<td>3632-4086g</td>
<td>33</td>
<td>15</td>
<td>29</td>
</tr>
<tr>
<td>&gt;4086g</td>
<td>20</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Birth height</td>
<td>/181</td>
<td>/49</td>
<td></td>
</tr>
<tr>
<td>&lt;46cm</td>
<td>13</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>47-52cm</td>
<td>104</td>
<td>58</td>
<td>59</td>
</tr>
<tr>
<td>&gt;53cm</td>
<td>64</td>
<td>35</td>
<td>33</td>
</tr>
<tr>
<td>Head circumference</td>
<td>/129</td>
<td>/38</td>
<td></td>
</tr>
<tr>
<td>&lt;33cm</td>
<td>35</td>
<td>27</td>
<td>21</td>
</tr>
<tr>
<td>34-37cm</td>
<td>87</td>
<td>67</td>
<td>74</td>
</tr>
<tr>
<td>&gt;38</td>
<td>7</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Gestational age</td>
<td>/208</td>
<td>/56</td>
<td></td>
</tr>
<tr>
<td>26-37wk</td>
<td>22</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>38-42wk</td>
<td>175</td>
<td>84</td>
<td>80</td>
</tr>
<tr>
<td>43-44wk</td>
<td>11</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Oxygen</td>
<td>43/208</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>Jaundice</td>
<td>99/223</td>
<td>44</td>
<td>40</td>
</tr>
<tr>
<td>Malformation</td>
<td>6/207</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Meconium</td>
<td>6/206</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>Aspirated</td>
<td>5/206</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Hydrocephaly</td>
<td>1/206</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cephalhematoma</td>
<td>4/206</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>36/209</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>Heart defect</td>
<td>9/207</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

#### 2.5 EPIDEMIOLOGY OF AUTISM- A REVIEW OF STUDIES IN THE 1990’S

Seven articles of the 1990’s were collected for the pooling of some epidemiological data on autism. Their results are summarized in table 2-4. A total number of seven studies during the years from 1991 to 1999 were collected for the analysis. There were a total number of 547 autistic subjects. As assessment of intellectual function was obtained for all these studies (Fombonne, 1999). The mean proportion of subject without any intellectual impairment was 25.9 (range:13.1 to
Table 2-4. Main characteristics of identified samples of the 1990’s

<table>
<thead>
<tr>
<th>Study, author, year</th>
<th>Number With autism</th>
<th>N</th>
<th>IQ% mild</th>
<th>Severe</th>
<th>Sex ratio M/F</th>
<th>Prevalence rate (/10,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnusson &amp; Saemundsen (1999)</td>
<td>40</td>
<td>15</td>
<td>50</td>
<td>35</td>
<td>34/6 (5.7)</td>
<td>10.4</td>
</tr>
<tr>
<td>Sponheim &amp; Skjeldal (1998)</td>
<td>34</td>
<td>47.1</td>
<td>52.9</td>
<td></td>
<td>23/11 (2.09)</td>
<td>7.2</td>
</tr>
<tr>
<td>Webb et al. (1997)</td>
<td>53</td>
<td>-</td>
<td>-</td>
<td></td>
<td>46/7 (6.57)</td>
<td></td>
</tr>
<tr>
<td>Fombonne et al. (1997)</td>
<td>174</td>
<td>12.1</td>
<td>6.6</td>
<td>81.3</td>
<td>112/62 (1.81)</td>
<td>5.35</td>
</tr>
<tr>
<td>Honda et al. (1996)</td>
<td>18</td>
<td>50.0</td>
<td>11.1</td>
<td>38.9</td>
<td>13/5 (2.6)</td>
<td>21.08</td>
</tr>
<tr>
<td>Fombonne &amp; du Mazaubrun (1992)</td>
<td>154</td>
<td>3.3</td>
<td>18.1</td>
<td>68.6</td>
<td>105/49 (2.1)</td>
<td>4.9</td>
</tr>
<tr>
<td>Gilberg et al. (1991)</td>
<td>74</td>
<td>18</td>
<td>28</td>
<td>54</td>
<td>54/20 (2.7)</td>
<td>9.5</td>
</tr>
</tbody>
</table>

50%). The mean figures for mild to moderate retardation was 22.8% and severe or profound MR was 55.1%. The male to female sex ratio varies from 1.81 to 6.57 with a mean value of 3.36 (3.36 males to 1 female). The prevalence rates range from 4.9 per 10,000 to 21.08 per 10,000.

2.6 RATES OF ASSOCIATED MEDICAL CHARACTERISTICS – THE FRENCH STUDY

Epidemiological data have been used to find out the prevalence of autism and its associated medical conditions. The data are important in identifying and designing special educational and medical services for these children (Fombonne et al., 1997). They performed an epidemiological survey on autism and its related medical conditions among 325,347 French children born between 1976 and 1985 in three different French regions. Their results are listed in table 2-5.
Table 2-5. Two surveys on associated medical characteristics with autism.

<table>
<thead>
<tr>
<th>Surveillance</th>
<th>Survey 1992-93</th>
<th>Pooled results of two surveys</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Autistic</td>
<td>Non-autistic</td>
</tr>
<tr>
<td></td>
<td>children (n=174)</td>
<td>children (n=5,926)</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>46</td>
<td>26.4</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>5</td>
<td>2.9</td>
</tr>
<tr>
<td>Sensory defects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blindness</td>
<td>5</td>
<td>2.9</td>
</tr>
<tr>
<td>Deafness</td>
<td>3</td>
<td>1.7</td>
</tr>
<tr>
<td>Blindness &amp; deafness</td>
<td>8</td>
<td>4.6</td>
</tr>
<tr>
<td>Congenital rubella</td>
<td>1</td>
<td>0.6</td>
</tr>
<tr>
<td>Disorders of known genetic origin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Down's syndrome</td>
<td>3</td>
<td>1.7</td>
</tr>
<tr>
<td>Fragile X</td>
<td>3</td>
<td>1.7</td>
</tr>
<tr>
<td>Chromosome abnormalities</td>
<td>2</td>
<td>1.1</td>
</tr>
<tr>
<td>Tuberculous sclerosis</td>
<td>2</td>
<td>1.1</td>
</tr>
<tr>
<td>Neurofibromatosis</td>
<td>1</td>
<td>0.6</td>
</tr>
<tr>
<td>PKU</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

Autistic children were more often affected with epilepsy (24.4%) than non-autistic children (10.6%). The rate of cerebral palsy, likewise, is higher for autistics than non-autistics. Sensory impairments were found to have no difference between children with autism and controls. The rate of Down syndrome among autistic children was significantly lower than in the comparison group. Other genetic disorders, other than Down syndrome and phenylketouria (PKU), had significantly higher values among autistic children than non-autistic children. Such disorders were fragile X syndrome (1.7 vs. 0.17), tuberous sclerosis (1.1 vs. 0.10), neurofibromatosis (0.6 vs. 0.08).

The 1992-1993 survey was conducted with a large sample and the prevalence was determined to be 5.35/10,000. This value was consistent with most other surveys.
Fambonne et al. mentioned a point that there had been little empirical attention to the possible increase of the prevalence of autism. But the two surveys did not have a rise in the prevalence of autism. The two survey results (survey 1992-93 and survey 1985-93) showed very similar results for the prevalence rate of various medical conditions associated with autism. PKU did not occur to have significant values in both surveys. Similarly, neurofibromatosis had very low (0.3%) value. The prevalence of Down syndrome was significantly lower in the autistic group than in the normal group. Such an atypically low prevalence rate for Down syndrome may well be an indicator of a diagnostic misclassification of autism and mental impairment. The association between tuberous sclerosis and autism did not appear strong as indicated in table 2-5. Fragile X syndrome, however, appeared to be more prevalent among autistic boys with a prevalence of 1.7%. This is very close to the 1.6% as reported by Bailey et al. (1993) in their autistic twins and singletons study. In short, epilepsy appeared to have a strong association with autism and its prevalence rate was well above the prevalence rates of other medical conditions studied.

2.7 ASSOCIATED MEDICAL CONDITIONS- OTHER STUDIES

The epidemiological data from the French studies were quite significant considering of their large sample size. It is also worthwhile to look at results from other investigations. The prevalence rates of some medically associated conditions with autism are pooled from five different surveys and their results are summarized in table 2-6. The mean rates and ranges for each disorder are: 17.6% for epilepsy (range: 4.8-23.6%), 1.5% for tuberous sclerosis (0.4-2.9%), 1% for neurofibromatosis (0.6-1.4%), 2.3% for Down syndrome (0-5.9%), 0.7% for congenital rubella (0.0-
1.3%), 3.12% for hearing impairment (0.9-5.8%) and 1.4% for visual impairment (0.0-2.9%).

A major drawback of these pooled results was that the sample sizes of some investigations were quite small. Nevertheless, the results consolidated the scientific knowledge on the association between autism and known medical conditions. Congenital rubella and PKU had almost no case of autism. This agreed with the results from the French epidemiological studies in table 2-5 (Fambonne et al., 1997). Neurofibromatosis, similarly, had a low prevalence rate of 1% and was almost identical to the result of the French studies. Cerebral palsy and Down syndrome were shown to have prevalence rates of 2.93% and 2.3% respectively. Fambonne et al. suggested that the high rate of mental impairment among autistic individuals might render such values insignificant. That is, there is no particular association between autism and cerebral palsy and Down syndrome.

Unlike cerebral palsy and Down syndrome, the low rates of fragile X and tuberous sclerosis were underestimated, according to Fombonne (1999). He describes the low rates for fragile X syndrome was because of the unrecognition of the problem until recently and the rare systematic screening of the genetic defect. Tuberous sclerosis, likewise, had an abnormal low rate in this pooled analysis than other studies (Smalley et al., 1992; Gillberg et al., 1994). The rates of epilepsy were high (17.6%) among the pooled samples; however, these values were underestimated of the lifetime risk of epilepsy in autistic individuals (Fombonne, 1999). Volkmar & Nelson (1990), described that the rates truly reflected the incidence of epilepsy in autistic children.
Table 2-6. Pooled epidemiological data of some associated medical characteristics of autism

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Epilepsy</th>
<th>N</th>
<th>%</th>
<th>Cerebral palsy</th>
<th>N</th>
<th>%</th>
<th>Fragile X</th>
<th>N</th>
<th>%</th>
<th>Tuberous sclerosis</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bryson et al. (1988)</td>
<td>1</td>
<td>4.8</td>
<td></td>
<td>4.8</td>
<td></td>
<td></td>
<td>2</td>
<td>0.9</td>
<td></td>
<td>1</td>
<td>0.4</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Ritvo et al. (1989)</td>
<td>34</td>
<td>14.6</td>
<td></td>
<td>4.8</td>
<td></td>
<td></td>
<td>2</td>
<td>0.9</td>
<td></td>
<td>1</td>
<td>1.4</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Gillberg et al. (1991)</td>
<td>17</td>
<td>23.0</td>
<td></td>
<td>1.4</td>
<td></td>
<td></td>
<td>6</td>
<td>8.1</td>
<td></td>
<td>1</td>
<td>1.4</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Fombonne &amp; du Mazubrun (1992)</td>
<td>34</td>
<td>22.0</td>
<td></td>
<td>2.6</td>
<td></td>
<td></td>
<td>1</td>
<td>0.6</td>
<td></td>
<td>2</td>
<td>1.3</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Sponheim &amp; Skjeldal (1998)</td>
<td>8</td>
<td>23.6</td>
<td></td>
<td>2</td>
<td>0.0</td>
<td></td>
<td>0</td>
<td>0.0</td>
<td></td>
<td>1</td>
<td>2.9</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>mean x</td>
<td>17.6</td>
<td>2.93</td>
<td></td>
<td>3.2</td>
<td></td>
<td></td>
<td>1.5</td>
<td></td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PKU</th>
<th>N</th>
<th>Neurofibromatosis</th>
<th>N</th>
<th>%</th>
<th>Down's syndrome</th>
<th>N</th>
<th>%</th>
<th>Congenital rubella</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritvo et al. (1989)</td>
<td>1</td>
<td>1.4</td>
<td>6</td>
<td>2.6</td>
<td>2</td>
<td>6</td>
<td>1.3</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Gillberg et al. (1991)</td>
<td>1</td>
<td>1.4</td>
<td>0</td>
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<td>0</td>
<td>0.0</td>
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<td></td>
</tr>
<tr>
<td>Fombonne &amp; du Mazubrun(1997)</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
<td>1.3</td>
<td>2</td>
<td>2</td>
<td>1.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fombonne et al. (1997)</td>
<td>0</td>
<td>0.0</td>
<td>3</td>
<td>1.7</td>
<td>1</td>
<td>1</td>
<td>0.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sponheim &amp; Skjeldal (1998)</td>
<td>0</td>
<td>0.0</td>
<td>3</td>
<td>1.7</td>
<td>1</td>
<td>1</td>
<td>0.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean x</td>
<td>0.0</td>
<td>1.0</td>
<td>2.3</td>
<td>0.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hearing Impairments</th>
<th>N</th>
<th>Sensory impairments</th>
<th>N</th>
<th>%</th>
<th>Visual</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sense of hearing</td>
<td>2</td>
<td>0.9</td>
<td>3</td>
<td>1.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sense of hearing</td>
<td>3</td>
<td>4.1</td>
<td>0</td>
<td>0.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sense of hearing</td>
<td>5.8</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sense of hearing</td>
<td>3.12</td>
<td>1.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sense of hearing</td>
<td>3.12</td>
<td>1.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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2.8 CONCLUSIONS

The investigation for specific causes for the syndrome of autism has yet to yield an answer. Research in epidemiology and molecular genetics will definitely provide more insight of this syndrome in the near future. Current diagnostic methods of interview and observation enhance the comparability across epidemiological surveys and between clinical samples. These data are valuable and useful for treatment and service considerations.
Chapter 3 Aetiology from the sociocultural perspective and medical perspective

3.1 INTRODUCTION

It has been 50 years since Leo Kanner first described autism as a distinctive pattern of symptoms in some children with severe development problems (Tonge et al., 1994). Many investigators have proposed several mechanisms as the aetiology of autism. One group considers that autism is genetically or biologically related; while another group considers it as a mental illness which is determined by parental deviance (Sauna, 1983). Most investigators before the early 1970's thought autism was psychologically related and was caused by some socialcultural factors. Later in the late 1970's, investigators shifted their focus to some structural inborn defects in the neuroanatomy and neurophysiology of the brain. Various findings suggest that autism is a disorder that encompasses both the subcortical and cortical levels of brain processing (Omitz, 1985). Other researchers, who also believe in the biological model, consider autism is a result of some pre- and prenatal trauma (Tonge at al., 1994). Most recent autism investigators further expand this biological model to the prospects of identifying the gene or genes in autism (Smalley and Collins, 1996). The investigation of the aetiology of autism has come a long way from the sociopsychological model to the neurobiological model and to the genetic model.
3.2 EARLY INVESTIGATION – SOCIALCULTURAL POINT OF VIEW

Most early investigators of autism, including Leo Kanner, who first described about the autistic syndrome in 1943, attributed the illness to environmental factors (Ornitz, 1983). Kanner himself thought the illness was related to some innate tendencies but at the same time to some parental deficiencies (Sauna, 1983). A few European studies hypothesized that parents of autistic children were of high socioeconomic status. Furthermore, these studies found definite social and educational differences among the parents of autistic and non-autistic children (Sauna, 1983). Ornitz, however, considers that several decades of research into autism have led to the conclusion that neither psychosocial and intra-psychiatric factors nor the abnormalities of parenting and family life contribute to the aetiology of autism (Ornitz, 1983).

3.3 THE MEDICAL MODEL – THE FUNCTIONAL NEUROANATOMY OF AUTISM

3.3.1 General neuropathology

Ornitz (1983) develops an approach to autism that permits the application of the neurophysiologic concepts, which according to him, is not as speculative as the sociocultural model. Autism is best viewed as a medical syndrome or a defined cluster of behaviours, signs, and symptoms which arise from diverse causes (Lotspeich and Ciaranello, 1993). There is evidence that the forebrain, brainstem, and cerebellum of autistic subjects are defective. In the forebrain, it was found there was some increase in cell densities in many areas of the limbic systems and in the cerebellar cortex, and a
marked reduction in the number of Purkinje cells and granular cells (Lotspeich and Ciaranello, 1993).

3.3.2 Foetal Circuitry

Current research points to the evidence that the brains of autistic subjects are often underdeveloped and immature (Gillberg, 1992). Bauman and Kempter (1989) speculated that the foetal circuitry (large neuronal cells) was retained for a time in younger autistic subjects. Such retained foetal circuitry may function initially, but it is not retained into adult life nor replaced by the adult neuronal patterns (Lotspeich and Ciaranello, 1993). Several neuropathological autopsy studies have demonstrated abnormal cell size, cell number, and persistence of immature developmental stages of the limbic regions, cerebellum, and brainstem (Lotspeich and Ciaranello, 1993).

3.3.3 Differences in the brain structure

3.3.3.1 Gyria malformation:

Piven and co-workers (1990) examined the cerebral cortex of four types of gyria malformations in 13 autistic subjects and 13 control subjects. The result showed that seven of the thirteen autistic subjects had one or more gyria malformation as a result from defects in the migration of neurons during the first six months of foetal development (Piven et al., 1990).
3.3.3.2 Brainstem:

The brainstem consists of three major structures: midbrain, pons and medulla oblongata (fig.3-1). Many investigators have looked at these various structures and the pons is the only structure that is found to have some differences in autistic subjects. Gaffney and co-workers (1988) found that the area of the pons and of the total brainstem were significantly smaller in the autistic group than in the control group; however, there is no significant difference in the areas of the midbrain and medulla oblongata.

3.3.3.3 Other areas of the brain:

A few investigators did studies on the comparison of the different areas of the brain between autistic and normal individuals. The results of these studies are summarized in Table 3-1.

<table>
<thead>
<tr>
<th>Finding</th>
<th>Source</th>
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<tbody>
<tr>
<td>Reverse L/R asymmetry of the forebrain</td>
<td>Hashimoto et al., 1989</td>
</tr>
<tr>
<td>Abnormally large lateral and fourth ventricle</td>
<td>Gaffney et al., 1987</td>
</tr>
<tr>
<td>Decreased area of sections of vermal lobules</td>
<td>Gaffney et al., 1987</td>
</tr>
<tr>
<td>And a decreased volume of the cerebellar hemispheres in some autistic individuals</td>
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Hashimoto et al. (1989) found that autistic and mentally impaired group had reversed left and right hemispheric asymmetry of the frontal lobes (right frontal lobes larger than the left frontal lobes) by means of MRI examination. Norwell and co-workers (1990) had a similar finding such that they identified reversed cerebral hemispheric asymmetry on axial, coronal, and saggital scans by qualitative measures. Gaffney and co-workers (1987) reported that the fourth ventricles (fig.3-1) were significantly larger in autistic group than in the control group; in addition, there was significant ratio differences between the fourth ventricle/cerebellum ratios and fourth ventricle/cerebrum ratio with the autistic subjects demonstrate a higher ratio. However, another investigator, Garber and co-workers (1989) found no significant differences between autistic and control groups in term of the size difference of the fourth ventricle. Murakami and co-workers (1989)
reported the same measurement of vermal lobules VI and VII between autistic subjects and found that they had smaller vermal lobules VI and VII (fig.3-2). Autistic probands are found to have smaller vermal lobules than the controls. To summarize, these results are rather conflicting and it is not conclusive that autistic subjects have any structural differences in the lateral and the fourth ventricles; however, the reversed L/R asymmetry is observed in several studies (Hashimoto et al., 1989; Norwell et al., 1990).

3.4 NEUROANATOMIC HYPOTHESIS

Ornitz (1983) suggested a neuroanatomic hypothesis to explain the behavioural component as a pathophysiology of the temporal lobe, various telencephalic structures, and the brainstem. Damasio and Maurer (1978) expanded this hypothesis by implicating other telencephalic structures like the mesial frontal lobes and the neostraitum in the pathology of autism. The neostratium consists of the caudate nucleus and putamen (fig. 3-3). Neurological symptoms such as dystonias, dyskinesias, abnormal muscle tone, and facial akinesia are indicative signs of the dysfunction of the neostraitum (Damasio & Maurer, 1978). Since the mesial frontal, temporal cortex and the neostratium are target structures of dopaminergic neurons, it is assumed that changes in the content of the dopamine can cause autistic behaviours (Ornitz, 1983).

The three behavioural problems of autistics are attentional deficits, akinesia and autistic motility. These deficits can be best explained with Damasio’s and Maurer’s hypothesis of the dysfunction of the cortical and neostriated structures (Ornitz, 1983).
Figure 3-2. Unfolded view (see upper right) of the cerebellar cortex showing lobes, lobules (by names and number), and main fissure. This specifies which lobules of the hemisphere (H) is continuous with its corresponding (by the numeral) vermal lobule. Murakami et al. (1989) reported that autistic probands have smaller vermal lobules VI and VII than control subjects.
Figure 3-3. Cross-section of the human brain from rostral (A) to caudal (D) showing the basal ganglia and related nuclei. Myelin stain.
Autistic disturbance in social relating, and communication; however, are best explained by the dysfunction of brainstem mechanisms which involves the vestibular modulation of sensation and motility (Ornitz, 1983). The sensory disturbances in autism are different from the symptoms seen in neurologic disorders in such a way that autistic subjects have both hypoactivity and heightened sensitivity to stimuli in all sensory modalities (Ornitz, 1983).

3.4.1 Vestibular dysfunction

Hypoactivity to auditory and visual stimuli are apparent in autistic children (Ornitz, 1983). For instance, sudden sounds may elicit no response at all in autistic children. They may visually ignore new persons or features in their environment and they may walk into objects as if they don’t see them. Painful stimuli, which may be especially significant from the dental perspective, are often ignored. They may not notice painful bumps, bruises, cuts or injections (Ornitz, 1983). However, some autistic children may get annoyed by the sound of some unusual objects such as the sounds of sirens, vacuum cleaners, and dog barking (Ornitz, 1983).

3.4.2 Autonomic and vestibular functions

Neurophysiological methods like EEG (electroencephalogram), event related potential (ERP), have been used to measure the sensory processing functions and the autonomic-vestibular functions of autistic subjects (Lotspeich and Ciarnello, 1993). Ornitz (1983) stressed the disturbance of sensory modulation early in development could cause the deviant social interaction and the deficient social communication in autistics.
Affected autistic children have the following characteristics:

1. A profound disruption of adaptive, integrative and motivated behaviours.

2. A lack of communicative skills.

3. The lack of applying past experiences to present transaction and future planning.

4. A lack of the sense of self.

5. A deficit in the adaptive use of imitative response, and the capacity to make motivated choices (Ornitz, 1983).

Ornitz suggested that these characteristics could be attributed from an inadequately modulated sensory input such that the child perceived external events and images inconsistently. Sensory input may be perceived in distorted form, randomly over- or under-amplified or filtered; consequently, the perceptual basis of the development of human relatedness is compromised. Autistic children do not sense the rest of the world like normal children do. Distorted perception of the environment may suggest that autistics are either receiving too little or too much sensory input. Vestibular and autonomic abnormalities were more likely to reflect a common brainstem mechanism which could be activated by many different aetiologies, including, on occasion, brainstem structural lesions (Ornitz, 1985).

3.4.3 Faulty sensory input and motor output

The autistic motility disturbances are also very specific to the syndrome (Ornitz, 1983). Some typical motor characteristics that are seen in most autistic children are:
1. Flapping movements of the lower extremities.
2. Engaging in an unusual body-rocking and swaying.
3. Head rolling.
4. Hold his/her hands in front of his/her eyes and writhe or twist the fingers and palms.
5. Repetitive, stereotyped wriggling of the fingers or the entire hand.
6. Whirl around the longitudinal body axis.
7. Bizarre posturing of the trunk or extremities.

Ornitz (1983) attributes such strange behaviour to the dysfunction of the central vestibular connection within the brainstem. Figure 3-4 shows a representation of the afferents from the ears to the vestibular nuclei in the brainstem. The vestibular system mediates motor activities through a network of receptors and neural elements. Some autistic children may show a defect in the vesicular stimulation by engaging in antigravity play, elevator rides, body whirling, rocking, swaying and head-rolling.
Figure 3-4. Afferents to the vestibular nuclei (Haines, 1997)

3.5 THE BRAINSTEM-VESTIBULAR HYPOTHESIS AND THE BRAIN Diencephalic Theory of Autism

Ornitz (1983) formulated the brainstem-vestibular hypothesis which is as known as the brainstem diencephalic theory of autism. The basic assumption is that sensory input is insufficiently modulated such that normal sensory information is not available for
processing by higher centres. The theory explains that the sensory modulation can be separated into three levels.

The first level of sensory modulation involves several structures of the vestibular system and the midbrain. It involves various structures of the vestibular system, the midbrain, and the interaction between the vestibular system and multilevel brainstem reticular formation centres. The reticular formation neurons respond to the stimulation from the vestibular nuclei efferents which, in turn, interact with neurons in the pontine and the ponto-medullary structures (fig.3-5) in the midbrain. These ponto-medullary structures control the eye movement. The rostral midbrain reticular neurons project back to the vestibular nuclei and to the labyrinths. The vestibulo-reticular system is induced by faulty sensory inputs in this model; there is experimental evidence for such vestibular dysfunction in autistic children.

The second level of sensory modulation involves the various mesencephalic structures and the neostriatum (caudate and the putamen see fig.3-2). This model explains that the medial thalamus receives sensory inputs from the somatosensory, visual, and vestibular systems. The combination of the dysmodulation of sensory input and the release of inappropriate motor behaviours suggests a secondary sensory modulation.
Figure 3-5. The orientation of the medical leminscus at all brainstem levels (Haines, 1997).
that involves a complex loop of mesencephalic structures such as, the medullary reticular
formation [MRF] and the substantia nigra [SN], the cento-median-parafascicular complex
[CM-PF] loop and the neostriatum. A neurophysiological system dysfunction in autism,
originating at the vestibular -ponto- medullary brainstem level, could be transmitted
through the pontine-mesencephalic reticular formation (MRF) polysynaptic pathway and
the vestibular efferents to the CM-PF polysynaptically to the caudate nucleus (see fig.3-6).
Such a disruption of sensory modulation cascade results in the disinhibition of
stereotypic motility patterns as seen in autistic patients.

The third pathway involves the sensory modulation from the reticular nuclei of the
thalamus to the MRF. The thalamus is a gate that interacts between specific thalamic
nuclei and the cortex. It is under the control of the brainstem reticular core, the CM-PF
and other non-specific thalamic nuclei. Ornitz hypothesized that the interaction between
this system and the more caudal levels of sensory modulation was the possible cascading
levels of sensory dysfunction which compromised the selective awareness of autistic
numerous studies and they found that autistic subjects had dysfunctional multisynaptic
paths in the brainstem.

3.6 SUMMARY OF THESE TWO HYPOTHESES

In summary, both the telencephalic and brainstem diencephalic hypotheses have
support from neurophysiologic research. As illustrated in figure 3-7, the autistic
Figure 3-6. A schematic representation of the modulation of sensory input impinging on several levels of the reticular formation, the non-specific thalamic nuclei, and the specific thalamic nuclei (Ornitz, 1983).
Figure 3-7. Autistic behavior falls into three broad categories—disturbance of relating, communication, and language, and sensory modulation and motility (Ornitz, 1985).
syndrome consists of three major clusters of behavioural disturbances: relating to people and objects, language and communication, and sensory modulation and motility (Ornitz, 1985). It is difficult to imagine how the disturbances of relating and language might be evoked by these sensory modulation and motility (Ornitz, 1985). These disturbances can be considered as consequences of perceptual inconsistency. Similarly, cognitive deficits among autistics could be explained by some distorted inputs (Ornitz, 1985); thus the autistic child cannot make sense out of the sensation of his or her surroundings (Ornitz, 1985).

3.7 FUNCTIONAL ASSOCIATION AND SPECTROSCOPY STUDIES

Several studies have investigated abnormal metabolic activities, functional dissociation and the clinical dysfunction of the brain cortex of autistic children. Horwitz et al. (1987) performed a functional association analysis between pairs of brain regions by means of Positron Emission Tomography. Functional associations are demonstrated by elevated metabolic activities (Lotspeich and Ciaranello, 1993). Horwitz et al. found autistic men had fewer functional associations than controls between regions of frontal and parietal lobes. The autistic group, furthermore, had shown to have a decreased functional association between the thalamus, head of the caudate nucleus, and the lenticulate nucleus (Horwitz et al., 1987).

Other researchers, similarly, found that autistic probands had abnormal levels of some metabolites than control subjects with the use of p-NMR spectroscopy. Minshew et al. (1989) performed an analysis of phosphorus metabolism in brains between autistic
men and control subjects. They noted the following results among the autistic subjects: decreased level of phosphomonoesters, increased levels of phosphodiesters, and decreased levels of ATP. These results are indicatives of decreased synthesis and/or increased breakdown of membrane phospholipids and increased utilization of ATP in the dorsal prefrontal cortex of autistic subjects (Lotspeich and Ciaramello, 1993). Minshew et al. (1989) concluded that these metabolic findings could explain the abnormal dendritic integrity of autistics and the clinical dysfunction of the association cortex.

3.8 CONCLUSIONS

- Early investigators of autism thought the illness was psychological and was caused by some family problems and parenting deficiencies.
- Later researchers demonstrated that autism was strongly related to some inborn structural deficiencies of the neuronal circuitry.
Chapter 4 Aetiology from the genetic perspective

4.1 THE INVESTIGATION OF THE AETIOLOGY OF AUTISM FROM THE GENETIC PROSPECTIVE - INTRODUCTION

In the 1970's, it was generally agreed that autism was an inborn disorder; however, there was still attempts to investigate the possible genetic influences. Flostein and Rutter (1977) reported on a systemic sample of twins with autism and showed that the concordance rate among monozygotic (MZ) twins was very much higher than among dizygotic (DZ) twins. They were the pioneers in approaching the aetiology of autism from the genetic prospective. They found that a family history of speech delay was common among autistics and they raised the possibility it was the genetic influence of some broader linguistic and cognitive impairment, which was inherited among autistics.

Flostein and Rutter (1977) also found that the abnormalities of language were much more frequent in the MZ than in the DZ twins. Such a difference in concordance rate points strongly to the importance of genetic factors in the aetiology of autism. The findings that concordance rate are strongly associated with the zygosity of the twin pairs and with the presence of physical environmental hazards. These hazards may cause biological damages during the birth process. This belief was generally agreed in the literatures of the late 1990's
because there was evidence that certain severe insults early in the prenatal development could increase the risk of autism (Szarmari et al., 1998). For instance, Stromland et al. (1994) evaluated the population of thalidomide embroyopathy patients in Sweden and found that four individuals met the diagnosis for autism. Both genetics and environment factors, consequently, are important in the aetiology of autism.

Folstein and Rutter (1977) concluded this primary investigation of the role of genetics in autism with two points. First, autistic syndrome is not a disease that is inherited in a clear-cut Mendelian fashion. Many factors such as genetic heterogeneity, high mutation rate, and incomplete penetrance may distort the simple Mandelian ratios. Second, environmental hazards from pernatal, perinatal and postnatal development play an important part in the cause of autism.

4.2. GENETIC INVESTIGATION OF AUTISM IN THE 1980'S

Autism appears to have been linked to a number of conditions such as trauma, infection and genetic disease. It is believed that they cause defects in the neurological system. No single specific injury, however, has been found especially to be associated with autism. If the entire birth process is considered as a "total birth optimally scored", autism does have an association with complications in the birth process (Folstein, 1985). Folstein (1985) observed that genetic factors may be important because there is a 50 times expected chance among the siblings of autistic children to suffer from the same conditions. In addition, he reported that autism strikingly aggregated in families such that 25% of autistic cases had a
sibling or parent with a history of delayed speech and other language disorder. She proposed a multifactorial explanation in the mechanism of the genetics of autism.

In the model, an underlying liability to autism exists as trait of unknown characteristics. This unknown liability may be the product of genetic and environmental factors (Folstein, 1985). Persons over this “threshold value” will have one or more phenotypic manifestations of autism. This multifactorial mechanism explained the observation, which was reported by Folstein and Rutter in 1977, such that it appeared that autism was a combination of genetic vulnerability to cognitive and language abnormalities, and the occurrence of perinatal injury. This suggested that when a genetic predisposition to cognitive and language difficulties was present, the additional occurrence of early life injuries might frequently result a child with autism (Folstein, 1985).

4.3 INVESTIGATIONS IN THE EARLY 1990’S

Autism researchers in the early 1990’s did numerous studies and further expanded our understanding of the role of genetics in the transmission of autism. Ozonoff et al. (1993) tested autistic siblings with the Winsconsin Card Sorting Test (WCST) and the Tower of Hanoi version 3 and 4 (TOH3 and TOH 4) in the measures of the cognitive abilities between siblings of autistic children and normal children. They found that the scores of autistic siblings were significantly depressed relative to control siblings on several measures of the WCST and TOH4. Therefore, they concluded that siblings of autistic probands were more identified as having cognitive difficulties than the control group. It appears also some genetic defects that are
transmitted in autistic families, perhaps in the executive brain domain, that is not transmitted in the control families.

4.4 STUDIES OF CLOSE RELATIVES OF AUTISTIC PROBANDS THAT LEAD TO THE Oligogenic MODEL

4.4.1 Social and communication deficits among the relatives of autistic probands

Bolton et al. (1994) made a flowchart (figure 4-1) to illustrate the communication deficit and repetitive stereotyped behaviours of autistics.

Figure 4-1. An illustration of the communication deficit and repetitive stereotyped behaviours of autistics (Bolton et al., 1994).
They did an assessment to check if relatives of these autistic probands had a deficit in social and communication skills. Their results clearly showed that milder forms of social and communication deficits were still aggravating in the relatives of autistic probands. And stereotyped behaviours were more than twice as common in the first degree relatives in the autistic group. These siblings of the autistic probands, in additions, had a much higher cumulative rate of disorders than the siblings of control groups.

4.4.2 Autism as a genetic disorder – twins studies

Investigators in the middle 1990’s have complied enough experimental evidence to show that autism is a strongly inheritable genetic disease. Bailey et al. (1995) suggested the oligogenic mode of autism inheritance. This model explains that autism may involve a relative small number of genes in its mode of genetic transmission. The concordance rate between monozygotic and dizygotic twins always have a big difference in which the MZ concordance rate for same sexed pairs is 60% and the DZ concordance rate is 0% (Folstein, 1996). Folstein (1996) agreed with the oligogenic model proposed by Bailey et al based on their finding of the same pattern of modest familial aggregation along with the very large MZ-DZ differences. They concluded that such a genetic pattern should be caused by 3 or 4 genes all together. In addition, such a drastic difference in concordance rate suggests that autism is a very strongly, highly inheritable, genetic neuropsychiatric disorder (Bailey et al., 1995; Folstein, 1996). Le Couteur et al. (1996) had similar findings such that the broader phenotype of autism was frequently found in the co-wins in MZ pairs but less frequently in the DZ pairs. From these observations and studies, it seems reasonable
to conclude that genetic factors account for the familial aggregation in families of autistic probands (Szatmari et al., 1998).

4.5 COGNITIVE PATTERNS IN PARENTS AND SIBLINGS OF CHILDREN WITH AUTISM

The prevalence of autism among siblings of autistic probands and the high frequency of cognitive deficits among parents of autistics all point show the importance of genetics in the transmission of autism. The rate of autism among siblings of autistic probands have been found to be 3-6% (Piven et al., 1990). Families studies, like Bolton et al. (1994) identified that some family members of autistics had some kind of cognitive impairment and appeared to exhibit a lesser or milder variant of autistic behaviours. Other family studies found the various genetic disorders such as phenylketonuria, tuberous sclerosis and fragile X syndrome are associated with autism (Boutin et al., 1997). The increase risk of autism among siblings of children with autism and less cognitive functioning of parents of autistic children provide evidence for the genetic basis of autism.

4.5.1 Autism and other pervasive developmental disorders among siblings of autistic children

Deficits have been reported in executive functioning (attentional flexibility, planning and working function) in siblings of autistic probands (Ozonoff et al., 1993). It was found that cognitively affected siblings clustered in about 20% of the families studied and were related to moderately or severely retarded autistic probands (Fambonne et al, 1997).
Autistic siblings had been identified to have significantly depressed intellectual abilities as measured by the Winsconsin Card Sorting Test (WCST) and Tower of Hanoi (TOH3 and 4). They reported that there was something transmitted in autistic families, perhaps falling in the executive function domain, which was not transmitted in control families (Ozonoff et al., 1993). Other reports also found that autistic siblings had defective cognitive abilities. One study by Fambonne and co-workers (1994) found that siblings did show a statistically significant deficit on both verbal and full scale of a cognitive test and these siblings also showed a significant increase in reading difficulties. DeLong and Dwyer (1988), similarly, reported that there was a language delay in 8% of the first-degree relatives of autistic probands with the use of a developmental history questionnaire. Piven and co-workers (1990) found learning disabilities, language delay, mental retardation, and/or autism in 15% of siblings of 37 autistic adults. Bolton and co-workers (1994) suggested a concept of severe forms of autistic illness in the siblings of autistic probands which he termed "phenotypic expression" of the hypothetical lesser variant. They found 12-20% of siblings of autistic probands exhibiting this lesser variant. Such a lesser variant of autistic behaviour includes communication deficits like language delay, reading retardation, articulation disorders, and spelling difficulties (Bolton et al, 1994). Consequently, these results suggest some kind of an association between autism and family history of cognitive disorders.

4.5.2 Parents of autistic probands

Other than twin studies and siblings studies of autistic probands, investigation of the cognitive function of parents of these autistic children also
showed that autism was a strongly inheritable genetic disease. Hughes and co-workers (1997) included a study that compared the parents of autistic children with parents of learning disabled children and a control group of adults from unaffected families on computerised tasks. They reported confirmation of the hypothesis that parents of autistic children showed impaired executive function (Hughes et al., 1997). Furthermore, these parents in the autistic group did appear to be less attentive and less motivated than control groups and they also showed to have worst performance on tasks that required both verbal and pragmatic skills (Hughes et al., 1997). These characteristics of parents of autistic groups are in accord with Folstein’s & Rutter’s (1977) and Folstein’s (1996) notion of autism of a lesser variant. These results, consequently, suggest autism is genetically inherited.

Other than twins studies, siblings studies of autistic probands, studies of the cognitive function of parents of autistic children also showed that autism was a genetic disorder. Hughes and co-workers (1997) included a study that compared parents of autistic children with parents of learning disabled children and a control group of adults from the unaffected on their performance of some computerised tasks. They reported of a confirmation of a hypothesis that parents of autistic children showed impaired executive function (Hughes et al., 1997). Executive function is defined as the frontal lobe functioning underlying goal-directed behaviours like planning, working memory, inhibition of potent responses, and cognitive flexibility (Hughes et al., 1997). Parents of the autistic group were shown to have worst performance on tasks that require both verbal and pragmatic skills. These characteristics of parents of autistic groups do match up with Folstein
and Rutter (1977) notion of autism of a lesser variant. They generally are described to have subtle peculiarities like language-based cognitive impairments. Some parents of autistic probands were found to have major affective disorders, specific mood disorders, with and without hypomania (Smalley et al., 1995).

4.6 CHROMOSOMAL ABNORMALITIES IN AUTISTIC CHILDREN

4.6.1 General

Studies of chromosomes can be very helpful in the search for the aberrant genes in neuropsychiatric disorders, like autism and autistic-like conditions, with a presumed genetic background (Gillberg, 1988). Jayaker and co-workers (1980) suggested that chromosomes had some fragile sites and they might be important in the underlying predisposition to autism.

Chromosome 1 and 2 have been identified to carry some aberrant alleles that are directly linked to autism. Halal and co-workers (1990) reported that terminal deletions of the long arm of chromosome 1 (del 1q) caused a characteristic combination of mental retardation and autistic type hand flapping, head-shaking, gaze avoidance, muteness, shrill cry and lack of emotionality (Gillberg, 1998). Wenger and co-workers (1987) also reported a patient with chromosome 1 deletion of an arm (1p del 35) and the patient suffered from learning disability and mental retardation and he subsequently ended up in a special education class for autistic children after several hospital evaluations. Chromosome 2, similarly, has been reported to carry some fragile sites that are related to the cause of autism. A fragile site called fra (2) q13 in chromosome 2 was identified in individuals with autistic behaviors (Jayakar et al., 1986). But
they raised a point that the causal link has yet to be proven because such fragile sites in chromosome 2 can also be found in phenotypically normal first degree relatives of affected individuals (Jayakar et al., 1986).

Chromosome 15 is another one that has been identified by many investigators to have abnormal sites that are directly linked to autism. One child was found to have an extra short piece of chromosome that matched up with the region 2 of chromosome 15 (Hopf and Bolton, 1995). This trisomy of chromosome 15 has been implicated in the genetic basis of dyslexia, which is one of the features of the lesser variant associated with autism (Bolton et al., 1994). This inverted-duplication of chromosome 15 may interfere with some specific aspect of brain development and function such that the disturbance leads to autism (Hopf and Bolton, 1995).

Aberrations of chromosome 15, as reported by Schroer et al. (1998) may be the single most common identifiable cause of autism. These aberrations include duplication & deletion involving of the long arm of chromosome 15 (Schroer et al. 1998) and the trisomy of region 2 of chromosome 15 (Hopf and Bolton, 1995). In the duplication-deletion model, it can take in one of the three forms (fig. 4-2): supernumerary inverted-duplicated 15 (inv dup 15q), supernumerary deleted chromosome 15 (del 15q), and interstitial duplication of proximal 15q (Schroer et al., 1998). Supernumerary dicentric 15 is defined as an inverted duplication of chromosome 15. Some phenotypes that have been reported among this aberration category are: delayed development, abnormal gait, awkward, unsteady, clumsy
behavioral disturbances (Schroer et al., 1998). Assumpcao (1998), similarly, classified these chromosomal aberrations into four groups, depending

Figure 4-2. Different types of chromosome aberrations – the abnormal chromosomes are indicated by arrows. a: supernumerary inv dup 15. b: with supernumerary deleted chromosome 15. c: with interstitial duplication of proximal 15q. d: with interstitial deletion of proximal 15q (Schroer et al., 1998).

on whether or not there has been a loss of chromosomal material (deficiency), fusion of a segment in the overturned position (inversion), fusion of a segment at another location (translocation), or duplication of the material (duplication). The
association of autism and inv-dup 15 appears to be real (Schroer et al., 1998) and many reports have shown their association.

Another two defects of chromosome 15, interstitial 15q duplication and 15q deletion (del 15q) are known to be linked to the etiology of autism. These defects are defined as parts of the alleles of chromosome 15 are duplicated or deleted. The duplicated alleles were reported to be maternally derived (Schroer et al., 1998).

Schroer and co-workers (1998) provided a plausible biological basis for variability in clinical phenotypes resulting from these duplication-deletion models of gene defects in the 15q region. Maternally derived duplication or deletion of the alleles (with or without inversion), in which the derived traits are dominant, may consistently produce abnormal phenotypes in the offspring (Schroer et al., 1998). However, paternally derived duplications and deletions of this region, provided that these alleles are recessive, will produce offspring that are phenotypically normal (Schroer et al., 1998).

4.6.2 Fragile X syndrome and autism

Fragile X (fra X) is a cytogenic marker located at site 27.3 on the X chromosome (X q27.3). This site is strongly associated with the fragile X syndrome (Folstein and Piven, 1991). The fragile X site has been known to be closely associated with mental retardation (Turner et al., 1986) and autism (Brown et al., 1986). The frequency of occurrence of autism among fra (X) males is 12.3%
(Brown et al., 1986). The mothers of these autistic fra (X) males are most likely to be carriers (Brown et al., 1986) and therefore, the chromosome with this fragile site is maternal origin.

Hagerman and co-workers (1986) performed a study of fifty autistic males with fragile X syndrome and their abnormal behaviors. They found 49/50 patients who demonstrated an onset of developmental problems before 30 months of age (Hagerman et al., 1986). All had delayed motor and speech development, difficulties in relating to others, gaze aversion, eye avoidance, shyness, tactile defensiveness, and occasional difficulty (Hagerman et al., 1986). Furthermore, they found that 44% demonstrated a lack of responsiveness early in childhood, such as failure to cuddle, no social smile, stiffening when held, withdrawal from social contacts, and extreme tactile defensiveness (Hagerman et al, 1986). Also, about 96% of these 50 patients had significant delays in language and speech peculiarities like echolalia, palilalia, preservative speech and dysfluencies. Echolalia is a pathological repetition or words spoken by another person and palilalia is a disorder of speech in which a word is spoken by the individual is rapidly and involuntarily repeated. In the study sample of Hagerman et al. (1986), a great number of subjects with the fragile (X) genotype demonstrated to have various autistic stereotypic behaviors.

In addition, Hagerman and co-workers (1986) found that 16% of the fra (X) patients had autism and this suggested a strong association of autism with the X chromosome disorder. Even though the fra (X) syndrome displays a strong association with autism, Hagerman et al. (1986a) suggested that is only one of the
diseases or one of the causes of autism. Many other organic disorders, such as congenital rubella, Rett syndrome, hyperarrhythmia, congenital infections, phenylketouria, and tuberous sclerosis cause global cerebral dysfunction and usually there is about 10% of patients in each diagnostic category develop autism (Hagerman et al., 1986).

Investigators of autism have well described the association of autism and fra (X) in males but not in females (Hagerman et al., 1986). As expected with X-linked traits, this common familial form of fra(X) is more prevalent among males than females; estimates of its prevalence among males have varied from 0.90/1000 to 0.92/1000 (Ho et al., 1988). Hagerman and co-workers (1986) found two women with fra (X) syndrome and autism. Each woman clearly had the fra(X) syndrome physically, cytogenetically, and cognitively (Hagerman et al., 1986). However, the extent of the cognitive impairment associated with fra (X) is somewhat variable (Folstein and Piven, 1991).

Assumpcao (1998) suggested a mechanism how these aberrations occur in various chromosomes. During the cellular interphase, chromosomes are highly distended and active; consequently, they are more vulnerable to environmental changes which may cause ruptures in their structure. Such ruptures may be caused by radiations, infections, chemicals, or metabolic variations. When these chromosome lesions occur during the period of DNA synthesis, they affect the single-filamented chromosomes with the fractured parts fused together and go unnoticed.
Konstantareas and Homatidis (1999) studied 127 children who were diagnosed with autistic disorders, eight of them (63%) showed to have chromosomal abnormalities. This is close to the rate of 5% reported by Bailey et al. (1995). These results and some of the karyotypes are included in the following case study for the illustration of the principles of chromosome abnormalities that have been presented in this chapter so far.

4.6.3 Case study

Case A.W (figure 4-3A-G): The central portion of chromosome 2 was inverted (pericentric inversion of 2 with breakpoint at p11 and q13), one chromosome 3 had an elongated long arm (3 q+) and additional chromosomal material had been inserted at band 3q23 of chromosome 3 (Konstantareas and Homatidis, 1999). Therefore, the karyotype is

46 XY, inv (2) (p11, q13)pat, 3q+

Case S.B. (figure 4-4): Centrometric banding showed a 47XX + Inv-dup (15) chromosome complement.

Case J.C. (figure 4-5): Chromosome testing revealed a karyotype of 47 XY+ der (15). An additional bisatellited chromosome, composed of 2 acrocentric chromosome. Each cell type revealed the presence of a chromosome 15 short arm at both ends of the additional chromosome. A partial trisomy of the long arm and tetrasomy of the short arm of chromosome 15.
Figure 4-3A-G. A.W.'s karyotype. Note arrows at chromosome 2.
Figure 4-4. The karyotype of S.B. Note the extra chromosome next to chromosome 21 (Konstantareas and Homatidis, 1999).
Figure 4-5 The karyotype of J C. At the right of pair 15 note the presence of an additional chromosome 15
4.7 CONCLUSIONS

- Twin studies have shown that autism is a strongly inherited genetic disorder.

- Autism can be a result of multiple bio-physiological problems such as trauma and infections from the birth process, genetic defects inherited from parents and germ cell mutations from some environmental insults.

- Some fragile sites and aberrations on chromosomes have been identified. They are thought to have strong association with autistic behaviors in offspring that carries the genotypes.
Chapter 5 The management of autism from the medical and psychological perspective

5.1 MICHAEL – AN AUTISTIC ADOLESCENCE

Michael (an unreal name) was a 17 year-old adolescence who was diagnosed as having autism and mental impairment (Ghazinuddin et al., 1991). He was brought to the psychiatrist's office because of his persistent symptoms of frequent crying, social withdrawal, sleep disturbance, irritability and bad temper. Furthermore, he recently complained of physical fatigue and facial pain. The psychiatrist put him on fluoxetine (a serotonin reuptake inhibitor medication) 20mg/day. Four weeks later, Michael's parents reported his behaviour much better than when he was without the medication. He had the interest to join the family for meals and he seemed to be calm most of the day. During the course of his treatment, the medication was increased to 40mg/day; he was able to maintain his good mood and he did not suffer from any major side effects. His repetitive behaviour, nevertheless, persisted throughout the treatment period. Michael is an example of an autistic subject who receives benefits from pharmacological therapy. Other than serotonin uptake inhibitor medication, medical practitioners and pharmacologists have developed many other categories of drugs and supplements such as opioid antagonists and vitamin B6 with magnesium, to treat autism. Although the treatment results with medication are acceptable, but not entirely satisfactory. Autistic children who are on such
therapeutic regimens tend to be more amenable to behavioural modifications than those who are not on any medication.

5.2 METABOLIC APPROACH TO THE TREATMENT

Autism is a genetic disorder (Gillman and Tuchman, 1998). The genetic defects cause a series of metabolic disorders and a few of these disorders are associated with classic autism. They are phenylketouria (PKU), histidenemia, and neurofibromatosis. In some cases of autism, abnormal concentration of metabolites is seen among the affected individuals. Lis et al. (1976) reported that autistics had either a higher or lower excretion of uric acid than normal individuals, and they have abnormally high excretion of hippuric acid. Likewise, Voisconti et al. (1994) observed that autistic individuals had an abnormally low urinary tyrosine. Shaw et al. (1995) also reported that the autistics whom they studied had excretion of unusual metabolites in their urine samples which may be microbial origin. All these research findings have shown that autism may be a result of disorders in some metabolic pathways.

5.2.1 Ribose and uridine therapy – for nucleotidase-associated autism

Nucleotidase-associated autistic disorder (AD) is caused by an increase of cellular purine and pyrimidine 5'-nucleotides (Page, 2000). Theordore Page (2000) describes the behavioral symptoms are extreme hyperactivity, impulsivity, short attention span and a lack of interest in social interaction. All patients, according to Page, with such disorders have noticeable delay in language acquisition. If some speech is present, it is limited,
slurred, poor choice of words, and full of short telegraphic sentences. Some of these patients have neurological symptoms such as seizure, ataxia, awkward gait, and impaired motor outputs. In addition, they have frequent sinus and middle ear infections.

Page (2000) indicated that all these nucleotide-associated AD patients had six to ten folds increase in the hydrolysis of purine and pyrimidine 5' nucleotides. A treatment strategy is intravenous (IV) immunoglobulins administration to improve the immune functions, and the neurological-behavioural symptoms that are associated with the deficiency. Trials with ribose at 600mg/kg per day and uridine monophosphate (UMP) with cytidine monophosphate (CMP) at 150mg/kg per day showed significant decrease in seizures and other neurological symptoms in their autistic individuals. Page (2000) also reported another treatment trial with 100mg/kg per day of uridine showed to reduce ataxia, to improve gait and fine motor control, to increase attention and focus, to reduce compulsiveness, to improve pronunciation, to increase word retrieval and to have fewer infections among autistic children.

The mechanism for nucleotide therapies is not known. Similarly, the beneficial effects of uridine is not known either. Ribose and nucleotide therapies, most importantly, have shown some promising results on relieving some major autistic symptoms on affected individuals. Page (2000) speculates that if an increase in nucleotidase activity does cause a nucleotide deficiency in some autistic children, uridine supplements may produce a large amount of uridine monophosphate (UMP), which prevents the hydrolysis of other nucleotides. When there is a normal amount of nucleotides in the body, as Page
describes, autistic symptoms that are associated with nucleotidase-associated PDD (NAPDD) should be eliminated.

5.2.2 Low purine diet

Purine autism is a type of infantile autism with an excessive excretion of urate (Coleman and Gillberg, 1993). These patients have autistic characteristics that fulfill the criteria of classic infantile autism in the DSM-IV. Kleijen and Knipschild (1991) describe that 10-30 % of autistics actually have hyperuricosuria. Unfortunately, there has not been tremendous success in the treatment of hyperuricouric autism so far; however, autistics seem to have some beneficial effects from a low purine diet with or without allopurinol (Coleman et al., 1974). They reported that in several patients, low purine diet caused some increase in eye contact, social interaction, some improvement in language acquisition, and a reduction in self-stimulation. An attempt to replace the low purine diet with high purine diet in one patient, as described by Coleman et al. (1974) resulted in increased hyperactivity, and stereotypic behaviour and decreased social behavior.

5.3 PHARMACOLOGICAL TREATMENT OF AUTISM

5.3.1. Literature search

This part of the literature search was conducted with Medline with reference to articles dated from 1980 to 2000. They keywords used were autistic disorder and they were matched with various pharmacological therapies. Categories of drugs that were
generated were antipsychotics, serotonin reuptake inhibitors (SSRI), antianxiety drugs, psychostimulants, alpha-adrenergic agonists, and opioid drugs.

5.3.2 Pharmacology of antipsychotics

Gilman and Tuchman (1995) stated that antipsychotics, like haloperidol, were among the early medications used for the treatment of autism. The mechanism of action is the antipsychotics increase the dopamine turnover and thus decrease the concentration of dopamine at the synapse (figure 5-1). As shown in figure 5-1, haloperiodol acts postsynaptically on stimulating the release and uptake of dopamine. They suggested that children who were treated with the medication were calmer and easier to control.

5.3.3. Antipsychotic drugs

According to a review by Aman and Langworthy (2000), four kinds of antipsychotics have been commonly used to manage autism. They are haloperidol, fluphenazine, risperidone, and clozapine. Their findings and results are listed in table 5-1.

Nine reports were found and they all evaluated the effectiveness of antipsychotics on treating children with autism and other pervasive developmental disorders.
Figure 5-1. At the dopaminergic synapse, dopamine is released and reuptake into the neuron. It is believed that haloperidol and other antipsychotic agents increase the rate of dopamine turnover and thus decrease the concentration of dopamine in the neural circuit (Gudelsky G., 1998).
(PDD). Three were controlled studies (Anderson et al., 1984; Campbell et al., 1978; Lacascio et al., 1991), four were open design (Joshi et al, 1988; Harrigan & Barnhill, 1997; McDougle et al., 1997; Nicholson et al., 1998) and two were case reports (Zuddas et al., 1996; Malek-Ahmadi & Simmonds, 1998).

<table>
<thead>
<tr>
<th>Authors</th>
<th>Subjects</th>
<th>Drug Mean</th>
<th>Design</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campbell et al. (1978)</td>
<td>40 children AD</td>
<td>Haloperidol (1.65mg/day)</td>
<td>PBO controlled parallel 10wks</td>
<td>HYP decreased On task NS</td>
</tr>
<tr>
<td>Anderson et al. (1984)</td>
<td>40 children AD</td>
<td>Haloperidol (1.1mg/day)</td>
<td>PBO controlled parallel 4wks</td>
<td>HYP decreased carpet activity NS</td>
</tr>
<tr>
<td>Joshi et al. (1988)</td>
<td>12 children 8 PDD</td>
<td>Haloperidol (0.04mg/kg)</td>
<td>Open trial</td>
<td>HYP decreased</td>
</tr>
<tr>
<td>Lacascio et al. (1991)</td>
<td>125 children AD</td>
<td>Haloperidol</td>
<td>Crossover parallel</td>
<td>HYP improved</td>
</tr>
<tr>
<td>Zuddas et al. (1996)</td>
<td>3 AD</td>
<td>Clozapine 200-450mg/day</td>
<td>Case report</td>
<td>HYP improved</td>
</tr>
<tr>
<td>Horrigan &amp; Barnhill (1997)</td>
<td>11 AD</td>
<td>Risperidone (1.0mg/day)</td>
<td>Open trial 4 wks</td>
<td>HYP decreased</td>
</tr>
<tr>
<td>McDougle et al. (1997)</td>
<td>18 AD</td>
<td>Risperidone (1.8mg/day)</td>
<td>Open trial 12 wks</td>
<td>HYP decreased</td>
</tr>
<tr>
<td>Nicholson et al. (1998)</td>
<td>10 AD</td>
<td>Risperidone (1.3mg/day)</td>
<td>Open trial 12 wks</td>
<td>HYP decreased</td>
</tr>
<tr>
<td>Malek-Ahmadi &amp; Simmonds (1998)</td>
<td>1 AD</td>
<td>Risperidone (7.5mg/day)</td>
<td>Case report</td>
<td>less hyperactive</td>
</tr>
</tbody>
</table>

HYP = hyperactivity; AD = autistic disorder

All the studies involved the study of haloperidol and 38% of the subjects showed to be responsive. They all indicated a significant reduction in hyperactivity as assessed by the Children’s Psychiatric rating Scale (CPRS) (Overall and Campbell, 1988) and Conners’ Abbreviated Symptom Questionnaire (CASQ). Three out of the four reports on
haloperidol were double-blind placebo studies. All of their subjects were solely autistic whereas other reports on haloperidol had subjects whose disorders were just in the category of PDD. That is, they had mental illnesses that were similar to autism but not exactly autism. Aman and Langworthy (2000) criticized that those reports without placebo-controlled design may contain bias results. Nevertheless, all these studies suggested antipsychotic drugs did produce some mild to moderate medical benefits.

5.3.4 Drug information of neuroleptics for dentists

The medication haloperidol is an antipsychotic agent and a sedative. It is primarily used for the treatment of psychosis, behavioral problems, and treatment for infantile autism (Lacy et al., 2001). Some drug interactions, that are related to dentistry, are its additive CNS depression with narcotics. Dentists, therefore, must be careful when they have to prescribe analgesics with narcotics to autistic individuals who are on haloperidol. According to Lacy et al. (2001), the action mechanism of haloperidol is that it blocks the postsynaptic mesolimbic dopaminergic D1 and D2 receptors in the brain. Gillman and Tuchman (1995) criticized the long term use of haloperidol because most of the data were not been well-documented. And so, they encouraged the use of this drug on a short term basis only. This medication, also, exhibits strong adrenergic and anticholinergic effects. Patients who take the drug will experience serious drowsiness, reduced motor control, and xerostomia. Because of these undesirable effects, dentists should watch out for possible seizure, tardative dyskinesia, vomiting and xerostomia in autistic patients who are on haloperidol.
5.3.5 Pros and cons of the use of neuroleptics

Klein and Slomkowski (1993) listed several benefits of neuroleptics on autistic children. First, neuroleptics allow better behavioral regulation and the autistic child becomes more manageable, less hyperactive and more controllable. Second, the medications have shown to reduce stereotypic behaviours, but they do not reduce the lack of social responsiveness and communication. Neuroleptics allow the patient to be calm; therefore, caretakers are able to provide them better care. Third, since the medication has shown to be highly effective on controlling some key symptoms of autism, the need of institutionalizing autistic children can be reduced.

Despite of the initial success of neuroleptics on autistic children, medical practitioners still view them as a second line therapeutic agent because of their serious side effects. The use of neuroleptics may produce adverse effects such as withdrawal kinesia (Armenteros et al., 1995), tardative kinesia, and cognitive impairment (Osman and Loschen, 1992). Armenteros et al. (1995) argued that tardative dyskinesia was more related to a deficit of the central nervous system from some pre- and perinatal birth complications. Individuals with such deficit are prone to adverse drug effects to the neurological system. Hence, the adverse neurological effects of neuroleptics may not occur to all autistic children.
5.3.6 Antipsychotics that are not included in the review

Other neuroleptics like amphetamines (a stimulant), methylphenidate (a stimulant), dextroamphetamine (a stimulant), and clomipramine (a tricyclic antidepressant) are not included in this review. The reason haloperidol was chosen because it was the earliest known medication that showed some positive effects on autistic children despite of its undesirable side effects. Haloperidol, in addition, is the most extensively studied agents in the treatment of autistics (Gillman and Tuchman, 1995).

5.4 SEROTONIN REUPTAKE INHIBITORS (SSRIs)

Besides neuroleptics, serotonin reuptake inhibitor medication is another class of drug that have been widely used to manage autism. The anterior cingulate of the brain is rich in serotonin receptors and these receptors have a role in the formation of restricted interests and the obsessive-compulsive behaviour of autism (Hollander et al., 1998). If such an hypothesis is true, the use of serotonin reuptake inhibitors will worsen autistic symptoms because it will enhance the synaptic level of serotonin (Hunsinger et al., 2000). Nevertheless, this idea has been tested and it appears not to be true. Studies have reported the beneficial aspects of SSRIs on autistic patients. Ornitz (1983) suggests that the central nervous system of autistic and other PDD affected individuals is altered. Monoamines such as serotonin (5HT) and other catecholamines have shown to involve in autistic symptoms because these neurotransmitters are responsible for behavioural disturbances (Martineau et al., 1992).
Abnormal levels of serotonin among autistics have been thought as the pathogenesis of pervasive developmental disorders (PDDs). Several investigators have indicated that hyperserotoninema is present in most autistics and the whole blood serotonin level may be elevated in these individuals. Studies have shown that more than 40% of autistic individuals have hyposerotoninema (Gilman and Tuchman, 1995). This observation is also seen in family members with depression, anxiety, and obsessive-compulsive disorder (OCD) (Hollander et al., 1998). SSRIs like fluvoxamine and fluoxetine have been suggested to be effective drugs for treating obsessive-compulsive disorder. The rationale for the treatment (figure 5-2) is that the dysregulation of serotonin (5HT) in the neurotransmission may be the pathogenesis of OCD (Price et al., 1987; McDougle et al., 1990). McDougle et al. (2000) describe there has been clear improvement and efficacy with SSRIs in treating patients with obsessive-compulsive disorder. Thus, all these results support the serotonin hypothesis. The investigators, furthermore, indicate that autistic and OCD patients do share some common characteristics like repetitive thoughts and behaviours. The dysregulation of serotonin has shown to play a role in autism (McDougle et al., 2000). It is logical that serotonin reuptake inhibitors should have its effects on autistic individuals. Up to the present, five SSRIs have been commonly prescribed for treating OCD and autistic disorder. They are clomipramine, fluvoxamine, fluoxetine, sertraline and paroxetine. Several investigators have studied the effects of fluvoxamine and fluoxetine on patients with autism. I will review their findings regarding these two medications.
Figure 5-2. Biochemical events at serotonergic synapse and the drug interplay at the synapse. Serotonin (5 hydroxytryptamine, 5HT) is found in the body by hydroxylation of tryptophan. After the release of the 5HT, it is recaptured by an active reuptake mechanism (Ganong, 1999). It is believed that SSRIs inhibit the reuptake of 5HT post-synaptic level.

5.4.1 Fluoxxamine and fluoxetine

5.4.1.1 Pharmacology

Fluoxetine is commonly known by the public as Prozac®. It is an antidepressant and is in the category of serotonin reuptake inhibitors (SSRIs) (Lacy et al., 2000). The medication is widely used to treat major depression, moderate to severe bulimia nervosa, and obsessive-compulsive disorder. Some known adverse reactions, which are relevant to the dental practice, are drowsiness, sedation, neuromuscular tremor, and xerostomia. Its mechanism of action is the drug molecules inhibit serotonin reuptake at the CNS neurons.
5.4.1.2 Studies on fluoxetine

Delong and co-workers (1998) reported a study of 37 children who were diagnosed to have infantile autism and was treated with fluoxetine (0.2-1.4 mg/kg/day). Their responses were measured in terms of their progresses in their behaviours, language, cognition, as well as social improvement. Twenty two out of thirty seven children were found to have benefits from fluoxetine and such positive responses were maintained for at least 21 months. A similar study by Cook and co-workers (1992) involved the treatment of 23 individuals in the age range from 7-18 year with fluoxetine with 20mg up to 80mg/day every other day. They reported that 65% of their testing subjects had positive responses. They further described these subjects had a decrease in their repetitive, compulsive and aggressive behaviours. Subjects of a younger age group, likewise, tended to sleep better, to make more eye contact, and to have more motor flexibility.

5.4.1.3 Case reports

McDougle and co-workers (1990) reported a case study of a 30 years old autistic male who was inflicted with OCD and was being treated with fluvoxamine. His case history is as follows:

T was a 30 year-old man who [was presented to McDougle et al.'s clinic for an] evaluation and treatment of obsessive thoughts and compulsive behaviours. [He] suffered hypoxia at birth following a difficult forceps delivery at 39 wks gestation...[When he was a child he was] extremely withdrawn and unresponsive to human contact...He was fascinated with numbers and with objects that had movable parts...the diagnosis of infantile autism was made at 2.5 of age.
This patient had been obsessed by wooden stick collection, extreme cleanliness, and fingernail trimming. He met the criteria of DSM-III-R for autistic disorder (American Psychiatric Association, 1987). He was successfully treated with fluoxetine at 50mg/day and the medication was titrated to effect at 150mg/day. His response was evaluated with the Clinical Global Improvement Scale (CGI), which measures the behavioral symptoms, and the Yale-Brown Obsessive Compulsive Scale (McDougle et al., 1990), which measure the severity of obsessive-compulsive symptoms. Patient T showed a drastic progress in his clinical behaviors and a clear reduction in his obsessive-compulsive symptoms. This patient described the changes: "something amazing has occurred...there has been a change in me. I want to do something with my life." His mother was very happy with the result, she said, "the rituals are nearly gone...[he] wants to attend the coffee or social hour to meet his peers, with whom he has rarely interacted" (McDougle et al., 1990).

Mehlinger and co-workers (1990) reported a similar case of a 26 year-old autistic female who was treated at the Rush-Presbyterian St. Luke's Medical Center in Chicago, Illinois, USA with fluoxetine at 20mg every other day. The 26 year-old white autistic female was initially presented as being socially alienated, having stereotypic and repetitive behaviours, having impaired language ability, and using negativistic language. When someone interrupted her ritual, she would burst into extreme anger and temper. Under the fluoxetine treatment, the parents noticed an improvement in her social behaviour in that she was more interactive, and treated people with socially acceptable manners. Her parents noted a dramatic decrease in her repetitive behaviours and her
temper outbursts. Mehinger and co-workers (1990) indicated fluoxetine was effective in the treatment of obsessive-compulsive and ritualistic behaviours of autistic individuals. Other medications like clomolpromine, imipramine, amitryptyline, propranol, fenfluramine, clonidine, and buspirone also have shown to be somewhat effective on autistic children. They all function at serotonergic synapses. Their information will not be discussed in this review.

5.5 OPIOID MEDICATION

5.5.1 Naltrexone treatment- Introduction

As noted in Chapter 3, Chamberlain and Herman (1990) stated that opioids, serotonin, and melatonin could be important neurotransmitters and their hypersecretion may play a role in the aetiology of autism. Animal studies showed that the injection of morphine into infant animals reduced their social attachment with their mothers (Panksepp et al., 1980). Research results on the topic of naltrexone and autism from 1987-1998 are summarized in table 5-2.

Several investigators have proposed naltrexone as a symptomatic treatment of autism (Kolmen et al., 1995). It is an opiate antagonist with a potent long-lasting effectiveness on many autistic behaviours like self-injurious behavior (Kars et al., 1990), stereotypies, hyperactivity and withdrawal while it also increases verbal production, and attentiveness (Campbell et al., 1988, 1993, 1990; Leboyer et al., 1988; Walter et al. 1990). The mechanism is based on the opioid-serotonin autism hypothesis such that autistics
have defects in the pineal-hypothalamic-pituitary-adrenal system. The system modulates the neural circuit with peptides, serotonin, and endogenous opioids (Chamberlain and Herman, 1990). According to the model, autism is associated with the hypersecretion of brain opioids like β-endorphin since autistics share many similar characteristics with opioid addicts. Naltrexone, which is an opioid antagonist, reverse the effects of this opioid agonist; therefore, autistic individuals have a decreased in their stereotypic behaviour and mental dysfunction (Feldman et al., 1998). Naltrexone has shown to have tranquilizing and stimulating effects in some autistic children (Campbell et al., 1986). The research group states that the tranquilizing effects of naltrexone cause a reduction in fidgety and uncooperative behaviour. In low doses (0.5kg/mg/day), it shows to have tranquilizing effects while in high doses (2.0mg/kg/day), it causes a reduction in stereotypies and social relation. Campbell and co-workers (1986) indicated that because of these beneficial effects, naltrexone is a desirable medication to treat autistic children who require pharmacotherapy.

Table 5-2. Research findings from 1987-1998 on the association of naltrexone with the reduction of autistic behavior.

<table>
<thead>
<tr>
<th>Research paper</th>
<th>NALTRAXONE TREATMENT OF SELF-INJURIOUS BEHAVIOR (SIB)</th>
<th>N</th>
<th>Date</th>
<th>Behaviour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herman et al. (1987)</td>
<td>3</td>
<td></td>
<td>0.5-2 0mg/kg</td>
<td>Dose dependent reduction up to 1.5 mg/kg</td>
</tr>
<tr>
<td>Leboyer et al. (1988)</td>
<td>2</td>
<td></td>
<td>1-2mg/kg</td>
<td>Decreased SIB except at 2mg/kg</td>
</tr>
<tr>
<td>Kars et al. (1990)</td>
<td>6</td>
<td></td>
<td>20mg/day for 3wks</td>
<td>Half of subjects showed reduction during 3rd week</td>
</tr>
<tr>
<td>Walters et al. (1990)</td>
<td>1</td>
<td></td>
<td>1mg/kg</td>
<td>Dramatic reduction of SIB with Some increase in social relatedness</td>
</tr>
<tr>
<td>Panskepp and Lessing (1991)</td>
<td>4</td>
<td></td>
<td>intermittent dose every 3rd day at 0.4-0.5mg/kg</td>
<td>Decrease in aggressiveness, negativism, aloofness, increase in physical and eye contact, language, bodily contact and play for 1 year</td>
</tr>
<tr>
<td>Kolmen et al. (1995)</td>
<td>13</td>
<td></td>
<td>1mg/kg for 2 wks drug/placebo</td>
<td>The majority of testing subjects against placebo showed modest global improvement</td>
</tr>
<tr>
<td>Kolmen et al. (1997)</td>
<td>24</td>
<td></td>
<td>1mg/kg 28 days with placebo</td>
<td>11/24 modest improvement of behavior but learning did not improve</td>
</tr>
<tr>
<td>Feldman et al. (1998)</td>
<td>24</td>
<td></td>
<td>1.0 mg/kg Drug/placebo 22wks</td>
<td>No difference between the naltrexone and communication. No improvement in communication</td>
</tr>
</tbody>
</table>
5.5.2 Research findings

Both Leboyer and co-workers (1988), and Kars and co-workers (1990) reported they had some success of the use of naltrexone on reducing autistic behaviors on some affected individuals. The administration of naltrexone on 2 autistic girls successfully reduced the degree of hyperactivity and self-injurious behaviour (SIB) and improved social behaviour such as increased eye-contact, smiles and interactions (Leboyer et al., 1998). Kars and co-workers (1990), likewise, showed a dramatic decrease in SIB frequency of their autistic subjects during the third week of naltrexone administration. They attributed the benefit of the medication to be their antagonizing effects on the opioid receptors according to the opiate-autism hypothesis which may be involved in the pathogenesis of SIB among autistic children.

Walter and co-workers (1990) reported a case study of the use of naltrexone to reduce the level of self-injurious behavior on an autistic boy. Although the sample size was small, it still showed some evidence that endogenous opiates may contribute to self-injurious behavior and social withdrawal symptoms as seen in autistic children. Their study showed that autistic patients had a dramatic decrease in their frequency of self-injury and panic attack. Furthermore, these subjects showed to have more social relatedness and emotion positive effects. Other positive behaviours, which were observed during the naltrexone period, were reduced social withdrawal, increased social use of language, and reduced use of negativistic language. Walter and co-workers discussed that stereotypical behavior and self-injurious behaviour may be some negatively
reinforced behaviours as a result of stress; hence, the increase of endogenous opioids may produce some internal reinforcing power to buffer the stress. Naltrexone is an effective treatment for certain autistic behaviors because it serves as an antagonist to the action of the B-endorphin.

Panskepp and Lensing (1991) had a positive experience with the use of naltrexone in treating children with autism. They observed a reduction in some typical symptoms of autism like hyperactivity, aggressiveness, self-injury, and stereotypes. Furthermore, they found that naltrexone promoted social behaviours like verbalization, seeking of social contact, and social exploration such as eye-contact, vocalization, pointing, smiling and playfulness. The two investigators also suggested the optimal dosage and some information regarding the administration of the medicine. Positive effects tended to appear 12 hours after the taking of the medicine; likewise, intermittent administration of the medicine (e.g. once every 3 days) at low doses seemed to be therapeutically beneficial than more frequent daily doses and of higher dosage. They suggested that the optimal dosage was between 1.0-1.5 mg/kg for the best elimination of self-injurious behaviour.

Among the studies that have been collected on the topic of naltrexone and autism, the studies by Kolman and co-workers in 1995 and 1997 seem to be the most comprehensive and their reports contained statistically reliable data with acceptable sample sizes. They employed the use of several accredited scales to measure the effectiveness of the medicine on autistic individuals. They were the Conners Global
Improvement rating of global impression (CGI), Conners parent/teacher rating scale, the naltrexone side-effect scale (SE), and the parent impulsivity-hyperactivity factor (IHF) (National Institute of Mental Health, 1985). Their data showed that naltrexone caused significant improvement in six aspects: parent CGI, parent IHF, parent SE restlessness, teacher CGI, teacher IHF, and teacher SE restlessness (Kolmen et al., 1995). Therefore, these measures on global improvement, hyperactivity, and restlessness showed subjects had significant clinical improvement during the naltrexone treatment period; all subject showed minimal adverse effects.

In a follow-up study in 1997 by Kolmen and co-workers, they reported eleven out of 24 subjects with AD were identified to show positive response to naltrexone (Kolmen et al., 1997). Clinical evaluation suggested some modest improvement in school behaviour and some decrease in hyperactivity, restlessness and disruptive behavior. They were no improvement in learning. They concluded that no medication like naltrexone had shown such consistent and satisfactory results on autistic children without serious side effects. As a result, naltrexone should be a drug of choice for autistic children with short attention span and hyperactivity (Campbell et al., 1988).

5.5.3 Naltrexone and communication skills

The improvement on communication skills during the naltrexone treatment is another aspect which has not been studied in detail until Feldman et al. in 1999. At a dose of 0.5mg/kg per day, they reported that autistic children did not demonstrate any improvement in their communication output, communicative acts, utterances, the choice
of words, and language maturity. These children also showed no decrease in the degree of echolalia. Similarly, Willemson-Swinkels and co-workers (1996) described that there was no change in communication skills in their double-blind placebo-controlled study of naltrexone on autistic children. Campbell and co-workers (1988), however, noticed some unproductive speech improvement of autistics when they were on naltrexone. Panskepp and co-workers (1991) also stated some development of useful speech in the four subjects whom they studied after three months of naltrexone administration. The results so far have seemed quite contradictory and non-persistent between different investigation groups.

Feldman and co-workers (1999) concluded that naltrexone treatment had not been associated with any improvement in communication among autistic children. Since impairment in communication does interfere with learning and social functioning, naltrexone may have its limited use in this aspect. However, if the learning and memory abilities are associated with hyperactivity and restlessness, this medication may be useful.

5.5.4 Drug information of naltrexone

Naltrexone is in the therapeutic category of narcotic antagonist (Drug Information Handbook, 2000-2001). Its mechanism of action is that it acts as a competitive antagonist at opioid receptor sites. Common adverse reactions in more than 10% of the population are insomnia, nervousness, headache, low energy, nausea, vomiting, and arthralgia. Naltraxone is not associated with any major undesirable side effect but it will cause
narcotic withdrawal symptoms, which are similar to the physical and psychological dependency that drug addicts experience. In addition, its bitter taste may prevent some children from accepting the mediation.

5.6 NUTRITIONAL THERAPY

5.6.1 Background information

Linus Pauling, a two times Nobelist, formulated the orthomolecular hypothesis in 1968 (Pauling, 1968). He stated that some metal illnesses and diseases were from some biochemical errors in the body. Pauling defined this approach as a treatment to restore the optimal concentration of substances that were supposed to be in the human body. In his view, each individual has his or her genetically governed factors in the needs for certain concentrations of essential substances such as vitamins and minerals in the body (Pfeiffer et al., 1985).

High doses of vitamins have been tested for many mental diseases in children like Down syndrome, hyperactivity, and mental retardation for the last five decades (Kleijen and Knipschild, 1991). Pfeiffer and co-workers (1995) found at least 30 studies that were related to megavitamin therapy and eight of these studies were involved autistic children. Their review of these studies will be discussed. Vitamins and minerals that have shown benefits to autism are vitamin B6 + magnesium and niacin (vitamin B3) (Kleijen and Knipchild, 1991). Other supplements like vitamin C, dimethylglycine, and other trace elements may also be beneficial to some autistic children. Since many autistic children have their peculiar preferences for food, it is not surprising that some of
them show evidence of nutritional deficiencies (Clark et al., 1992). In this section, research findings regarding the benefits of vitamin B6 and magnesium will be discussed.

5.6.2 Research findings

Research has found that vitamin B6 does have its benefits on managing aberrant behaviours of some autistic children. Hunsinger et al. (2000) cited a bar graph from Rimland's Autism Research Institute publication in 1999 (figure 5-3). It shows the parental assessment of various pharmacological and non-pharmacological therapies based on their response to the questionnaires. Many parents evaluated various supplements like calcium,
Figure 5-3. Parental assessment, based on the response to questionnaires, of the effects of drug or nutrients on the behavior of their autistic children (Hunsinger et al., 2000).

vitamin C, folic acid, vitamin B6 with magnesium, zinc and dimethylglycine (DMG) highly to equally effective to traditional pharmacological therapies. The parents described that these supplements improved their autistic children’s behavior. From this data, nutrient therapy has been rated to be equally- or more-effective than drug therapy (as cited by Hunsinger et al., 2000)
Pfeiffer and co-workers (1995) performed a review of clinical studies from 1980 to 1989 regarding the therapeutic effects of vitamin B6 plus magnesium in the treatment of autism (table 5-3).

<table>
<thead>
<tr>
<th>Study</th>
<th>Behavioral outcomes</th>
<th>Lab outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barthelemy et al. (1980)</td>
<td>Moderate therapeutic effect of B6/Mg but Mg alone had comparable effects</td>
<td>B6/Mg &amp; Mg alone decreased HVA levels</td>
</tr>
<tr>
<td>Barthelemy et al. (1981)</td>
<td>Significant decrease in autistic behavior</td>
<td>Significant decrease in uHVA</td>
</tr>
<tr>
<td>Barthelemy et al. (1983)</td>
<td>Behavior improved significantly on withdrawal, interest in people, aversion to physical contact, stereotyped behavior</td>
<td>Decrease in uHVA</td>
</tr>
<tr>
<td>Jonas et al. (1984)</td>
<td>Behavior improved significantly</td>
<td>Non-significant improvement in uHVA</td>
</tr>
<tr>
<td>Martineau et al. (1981)</td>
<td>6 out of 12 improved clinically</td>
<td>Increased in amplitude of middle latency EP's; decreased in HVA levels; significant inverse relationship between EP and HVA EPs</td>
</tr>
<tr>
<td>Martineau et al. (1986)</td>
<td>Improved in behavior; deterioration in behavior 6 wks after cessation of B6/Mg</td>
<td>Improvement in HVA levels and EPs</td>
</tr>
<tr>
<td>Martineau et al. (1988)</td>
<td>Significant improvement in global Behavior</td>
<td>Significant decrease in uHVA only in first 2 wks.</td>
</tr>
</tbody>
</table>

5.6.3 Other research findings

Several investigators (Barthelemy et al. 1980, 1981, 1983; Jonas et al., 1984; Martineau et al. 1981, 1986, 1988) have used homovanillic acid (HVA) as a laboratory measure index of how much vitamin B6 has improved the autistic symptoms. The rationale is that many investigations have shown HVA levels are abnormally high among autistic subjects and the administration of vitamin B6 does lower the HVA levels as well.
as improve the autistic symptoms (Barthelemy et al., 1981). An explanation from Dasmino and Maurer (1978) is that the deficient central nervous system of autistics causes a disturbance in the metabolism of dopamine, which produces HVA as a metabolite.

Another measure, evoked potentials (EP), was used by one of the investigators in Bathelemy’s summary of vitamin B6 research. Barthelemy and co-workers (1988) described that averaged evoked potentials (AEP) was the measure of the brain’s ability to process external sensory stimuli and catecholamine metabolism. The catecholamine system, in turn, has an important role in the control of brain functions such as motor control, cognition and hormonal release (Moore and Bloom, 1978). Barthelemy and co-workers indicate that AEPs may reflect abnormal dopamine functioning in autistic individuals and such dysfunctioning may link to autistic behaviour such as selective attention.

Five out of the six studies in table 5-3 used HVA to measure the effectiveness of vitamin B6-Mg in the alleviation of autistic symptoms. All these studies show the intake of vitamin B6 with Mg decreases the level of homovillic acid (HVA); thus all subjects have some notable improvement in their autistic behaviours except the study by Jonas et al. (1984). Similarly, the investigations by Martineau and co-workers (1985, 1986) showed a significant improvement in evoked potentials and the corresponding brain function after the administration of vitamin B6. All subjects showed a significant
decrease in their autistic behaviours. The results of all these studies concluded vitamin B6 appeared to reduce the aberrant behaviours of autistic individuals.

5.6.4 The importance of vitamin B6

Vitamin B6 is an important molecule in the body because it is the precursors of many neurotransmitters like serotonin (5HT), gamma-aminobutyric acid (GABA), dopamine (DA), norepinepherine (NE) and epinephrine (E) (Pfeiffer et al., 1995). Vitamin B6 exists as six biologically active forms: pyrodixine, pyridoxal, pyridoxamine, pyrodixine phosphate, pyridoxal phosphate, and pyridoxamine phosphate (Kleijen and Knipschild, 1991). As pyridoxal phosphate, vitamin molecules serve as coenzymes for a variety of amino acid metabolism. The two investigators mentioned that various neurological symptoms like convulsions, degeneration of peripheral nerves, dementia, hallucinations, and psychosis existed in patients with vitamin B6 deficiency. Pfeiffer and co-workers (1995) suspect that autistic individuals may have problems in the formation of these neurotransmitters and vitamin B6 can be a form of possible treatment. Kleijen and Knipschild in their 1991 paper mentioned an illness called homocystinuria which is a result of a B-synthase deficiency. Patients with this condition have mental retardation and behavioural disturbances very similar to autistic individuals. Braunwald and co-workers (1987) in the Harrison’s Principle of Internal Medicine stated that an administration of megadose of vitamin B6 (25-500 mg/day) appeared to relieve neurological symptoms in patients with homocystinuria. Vitamin B6 is relative inexpensive, and it will be wonderful if such therapy works on autism in which existing therapies are not satisfactory.
5.7 EPIDEMIOLOGY OF THE USE OF PSYCHOTROPIC AND VITAMIN THERAPIES

Aman and co-workers (1995) performed a questionnaire survey on 859 autistic individuals regarding the prevalence and patterns of use of some common medications prescribed for autistic children and adolescence. Their results are listed in table 5-4. Neuroleptics were among those that were prescribed the most with a 12.2% prevalence. A few other popular ones were psychostimulants with 6.6%; anxiohypertensive, 4.4%; and mood stabilizers, 3.9%. The investigation team also found that 19.2% of autistic individuals were on vitamins and 5% of them were on supplements, which were specifically in the market for the treatment of autism. Overall there was more than 50% of autistic patients who were on some sort of medication.

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroleptics</td>
<td>102</td>
<td>12.2</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>51</td>
<td>6.1</td>
</tr>
<tr>
<td>Mood stabilizers</td>
<td>33</td>
<td>3.9</td>
</tr>
<tr>
<td>Stimulants</td>
<td>55</td>
<td>6.6</td>
</tr>
<tr>
<td>Sedatives/hypnotics</td>
<td>53</td>
<td>6.3</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>37</td>
<td>4.4</td>
</tr>
<tr>
<td>Opiate blockers</td>
<td>3</td>
<td>0.4</td>
</tr>
<tr>
<td>Psychotropic drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>One drug</td>
<td>185</td>
<td>22.1</td>
</tr>
<tr>
<td>Two drugs</td>
<td>54</td>
<td>6.4</td>
</tr>
<tr>
<td>Three drugs</td>
<td>14</td>
<td>1.7</td>
</tr>
<tr>
<td>Four drugs</td>
<td>3</td>
<td>0.4</td>
</tr>
<tr>
<td>Total</td>
<td>256</td>
<td>30.5</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>111</td>
<td>13.2</td>
</tr>
<tr>
<td>Psychotropic drugs + anticonvulsants</td>
<td>326</td>
<td>38.9</td>
</tr>
<tr>
<td>Vitamins</td>
<td>161</td>
<td>19.2</td>
</tr>
<tr>
<td>Vitamins for autism only</td>
<td>42</td>
<td>5.0</td>
</tr>
<tr>
<td>Psychotropic drugs + autism vitamins</td>
<td>283</td>
<td>33.8</td>
</tr>
<tr>
<td>Psychotropic + anticonvulsants + autism vitamins</td>
<td>352</td>
<td>42.0</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>11</td>
<td>1.3</td>
</tr>
<tr>
<td>Any agent (psychotropic or other)</td>
<td>447</td>
<td>53.3</td>
</tr>
</tbody>
</table>
Aman and co-workers in 1995, furthermore, did a comparison of the patterns of use among different classes of psychotropic medicine. The use of neuroleptics, like haloperidol, were associated with several factors like age, severity of mental retardation, and type of housing than those who were not on haloperidol. The use of neuroleptics appeared to correlate with greater age, more severe autism, more severe mental retardation, and more restrictive housing. They explained that medical practitioners may be reluctant to prescribe neuroleptics to young autistic children and those, who were in residential care, were expected to be more unmanageable and uncooperative than those who lived at home. Consequently, they required potent medications to control their behaviours. In short, epidemiological research so far have shown the majority of autistics are on some sort of medication ranged from diet supplements to antipsychotic drugs.

5.8 BEHAVIOURAL MANAGEMENT OF AUTISM

Biochemical agents have been continuously developed in the last few decades to treat autism. Medication has shown to be effective in reducing behavioural symptoms of autistics and make them more manageable to behavioural modification, special education and psychosocial care (Campbell et al., 1988). An effective behavioural intervention should consist of four elements (Ann Le Couteur, 1990). First, the program has to be an accurate measure of the child’s actual skills and difficulties in the child’s natural environment. Second, the parents have to be involved in the identification of the target behaviour(s) to be modified. Third, the behavioural modification progresses in little steps.
Fourth, the most effective method should include a wide range of behavioural and educational methods.

LeBlanc (1993) indicates a seven step approach in the design of a successful behavioural management of autistic children. The approach guides professionals in the description, analysis and monitoring maladaptive behaviours. The seven steps are as followed:

1. Identify the behaviour that needs modification.
2. Describe the behaviour in quantifiable measurable terms.
3. Identify the ecological factors that will precipitate the occurrence of the behaviour.
4. Generate hypotheses regarding the nature and the function of the behaviour.
5. Set up short-term goals, and long-term goals.
6. Design an individualized custom made intervention.

Campbell and Schopher (1989) indicated a detailed analysis between the child and the environment such that an individual treatment plan could be set up for effective behavioural manipulation. This is particularly important for the development of adaptive behaviours and the elimination of maladaptive behaviour like aggression, self-injury, and self-stimulation (Campbell et al., 1996). LeBlanc (1993) introduced a four step method that emphasized on the description, analysis and monitoring of the maladaptive behaviour. First, one has to identify the behaviour that required intervention. LeBlanc defined this step as the identification of behaviour that are potentially dangerous to the child. Some dangerous behaviours like eye-poking, headbanging, putting objects into
ears, and serious headbanging. These behaviours have to be addressed and managed appropriately by individualized intervention plan.

Second, the caretakers have to describe the maladaptive behaviour in measurable terms. They have to use descriptors such as the frequency, duration, history and intensity of the behaviour as well as quantifiers like “when,” “where,” “how often,” and “magnitude” are to be included in the analysis. Third, one has to identify some ecological factors that precipitate the occurrence of the behaviour. Analyzing factors such as medications, medical problems, sleep cycles, eating habits, diet, daily schedule, the predictability, choice of activities, and sociological events are important in the understanding of the causes of maladaptive behaviour. Fourth, LeBlanc suggested that the investigators should generate hypotheses regarding possible functions of these maladaptive behaviour. For instance, in a case study as illustrated in figure 5-4, Bill may attempt to establish communication with the rest of the world with some seemingly awkward gestures and verbal messages. Similarly, Bill may attempt to escape from a boring task by being aggressive to others. LeBlanc further pointed out that autistic children like Bill had problems understanding the world and others did not understand him as well.

The fifth, sixth and seventh steps concern with the design of the intervention, the set-up of objectives, and the evaluation of its effectiveness. LeBlanc explained that each behaviour has to have its own intervention that specially targets at its modification. For
example, in order to avoid the subject’s aggression against others due to attention seeking, the caretaker may design personal booths to avoid such distractions.

The sixth step involves the immediate modification of the lifestyle of the subject and some specific interruption procedures when problem behaviour arise. In the last step, the result of the intervention is to be judged on the basis that the individuals has enrichment in the daily transactions with his environment. That is, the subject has increased social interactions thus the lifestyle is enhanced.
Case history: Name: Jim (not a real name), an autistic boy

From the parent’s view point, two main concerns are...minor self aggressive behaviour, specifically hand to head banging...seem to be associated with ...intensive interaction (arguments, loud voice, rough and tumble play. The second concern is running away behaviour. If this parent do not keep him under observation, he tries to escape, [the parents] observed [that he has] high tolerance to pain, he complains only when the pain is very intense. The behaviours of concern is the school environment are: the aggressive choking of other other students [ and his targets] are the weakest students. The third behaviour of concern is running away in escape from a task... (LeBlanc, 1993, P.94)

Step 1: Identify behaviours that require intervention
Identify: (1) Hand to headbanging – self injurious behaviour
(2) Running away behaviour – an escape
(3) Aggressive attack of other students

Step 2: Quantify the events
When? Intensive interaction ⇒ handbanging/ headbanging
When? Escape⇒ parents not observing him
When? Running away ⇒ escape from a boring task

Step 3: Identify conditions that will precipitate the occurrence of the maladaptive behaviours
Calm⇒ (progress to) ⇒ become agitated + excitement ⇒ aggression

Thus agitation and excitement are precipitators

Step 4: Generate hypotheses
- Eccentric behaviours as stimulation/non-stimulation
- Communication with the rest of the world – aggression on others?
- Escape – gets bored from a task
- Aggression – private space invasion by somebody’
- Aggression – frustration that he does not understand the world and the world does not understand Him
- Running away – control of his environment
- Self–injurious behaviour –“ I don’t understand this,” “ I can’t take this,” “Please explain.”

Step 5: Identify short-term objectives and long-term objectives
- Avoid escape motive: teaching tasks with verbal direction 2 times, verbal direction, gesture aids, demonstration, and hands-on/doing together
- Avoid aggression linked to the attention seeking motive: a personal working booth – prevents the distraction
- Frustration motive- symbolic communication for personal needs and environmental needs
- Running away – associate the running away behaviours as an exercise only.
- Minor self-aggressive acts – convince him that “he was playing,” “talking only.”

Step 6: Design of an individualized behavioural intervention plan
Immediate modification of the lifestyle of the subject and specific interrupted procedures, when problem behaviours arise

Step 7: Evaluate the impact of the intervention
5.9 CONCLUSIONS

- Some research shows that autism may be a result of some metabolic disorders. Various treatment modalities like ribose and uridine therapies, and low purine diet have been established.

- Medical practitioners have concentrated on the use of pharmacological agents in the management of autism. Medication like neuroleptics (haloperidol), serotonin reuptake inhibitors (fluoxetine), and opioid antagonists (naltrexone) have been widely used to manage children and adolescents with autism. Even though the use of these agents has had limited success, most investigators believe the use of these agents will make autistic children amenable to behavioural treatment.

- Some investigators have advocated the use of diet supplements to manage autism. Research so far has shown positive results with their uses on autistic children. Most parents and caretakers have rated nutrient therapy to be equally or more effective than drug therapy.

- Behavioural interventions remain as the mainstream of autism management. Various strategies have been advocated to enhance the lifestyle and modify maladaptive behaviours of autistic people.
Chapter 6  The management of autism from the dental perspective

6.1 DENTAL CARE AND AUTISTIC CHILDREN

Hugh Morgan (1996) in his book called "Adults with Autism" states that “preventive dental care is particular importance in avoiding the neglect of tooth and gum infections, which will produce considerable discomfort with secondary behavioural and nutritional problems.” Autistic children are particularly vulnerable to dental caries and gingival problems as a result of their peculiar eating habits, food preferences, nutritional deficiency, and bizarre self-injurious behaviour. People with autism tend to be uncooperative patients and a visit to the dentist can cause chaos in the dental office. Community dental services and practices, which provide experienced, empathetic, professional, and proper dental care for the patient with autism, are essential. In this chapter, the management of children and adolescents with autism from the dental prospective will be reviewed.

6.2 SURVEY OF ORAL NEEDS AND PROBLEMS OF AUTISTIC PATIENTS

6.2.1 The Long Island Jewish-Hillside Medical Centre Study

Autistic children and adolescents are special dental patients because they exhibit different dental and oral problems than other patients with developmental disability. Kamen and Skier (1985) quoted an investigation that was done by the joint effort of
the Niassan Suffolk Chapter of the National Society for Autistic Children and the Dental Department of the Long Island Jewish-Hillside Medical Center, New York. Their aim was to conduct a questionnaire survey (figure 6-1) to identify special oral needs of these hospitalized autistic patients. Table 6-1 summarizes the responses regarding the subjects' medical problems, special oral needs, oral hygiene practices, and dental experiences. In the responses, there is predominantly negative response to the questions of dental problems. Some probable reasons are the low incidence of dental caries among autistics, and the parents' low priority of giving their children dental care among other health services.

The questionnaire survey also indicates some interesting results regarding oral hygiene practices of autistic children and adolescents. Twenty-three out of 28 children brushed their own teeth but there were 19 out of 28 children also permitted their parents to brush their teeth. The result is thus quite mixed. Regarding flossing habits, Kamen stated that the total rejection of flossing indicated the attempt for such education by dentists was a total waste of time unless the child allowed a parent or attendant to perform the task.

6.2.2 Periodontal Status

Both Shapira and co-workers (1989) and Klein and Nowak (1999) performed some investigation on the topic of periodontal status of children and adolescents. Shapira et al. compared the periodontal severity and DMFT caries scores of 17 autistic institutionized adolescents, 15 non-institutionized autistic children and adolescents and 12 schizophrenic young adults. They found the majority of autistic subjects who were institutionalized had poor periodontal health and that 53% had
substantial amount of supra- and subgingival calculus. These subjects required thorough periodontal scaling and root planning and 47% of these in-patients had so severe periodontal problems that some forms of periodontal surgery was warranted. The non-institutionised autistics also had mild to moderate severity of periodontal problems but their severity was better than their institutionized counterpart. Shapira et al. attributed such poor periodontal health to their lack of patient cooperation, poor oral hygiene habits, and their fear of dental treatment.

Klein and Nowak (1999), likewise, reported similar results. They found 39.5% of the autistic patients had healthy gingiva, 51.2% had localized gingivitis, and 9.2% of them had general gingivitis. Overall, they reported that 85% of their group home patients had more pronounced periodontal disease than 50% of the younger patients who lived at home. Lowe and Lindermann (1985) also reported that their autistic group had a higher amount of food debris and calculus around their teeth than the non-autistic group. Furthermore, their autistic subjects demonstrated a higher plaque index, which was the presence of more plaque deposition, than the control subjects.

6.2.3 Caries prevalence and oral hygiene practices

Another epidemiological data that both research groups went into was caries incidence of children and adolescents with autism. Shapira and co-workers found that autistic children and adolescents, whether they were institutionised or non-institutionised, had less caries rates than the control subjects. They stated that the institutionized group has a 7.11 DMFT score and the non-institutionized group had a score of 8.73 while the control group, which was selected from some healthy and
normal children from the community, had a 11.63 DMFT score. Kopek (1977) describes autistics have their unique features in their food preferences. They often have a low desire for food with a high sugar content. He also considers such a unique preference for diet might contribute to their minimal amount of dental caries especially if they crave for a low carbohydrate diet. If the autistic child has a high preference for sweet food, he or she is expected to have a high caries rate. When comparing the caries index in autistic patients with deciduous dentition, Loe and Lindemann (1985) reported the autistic patients showed a significant higher caries index than the control subjects on initial examination. However, on recall exam, the autistic group did not show any increase caries rate than the control group.

Kopel also states that autistic children have some special eating habits like food pouching, refusal of solid food and chewing with mouth open. Klein and Nowak (1999) performed a survey of eating habits in the second part of the questionnaire. Their results are summarized in table 6-1.

<table>
<thead>
<tr>
<th>Subject of the question</th>
<th>Answers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Possible different eating pattern</td>
<td>Yes: pouching: 14%</td>
</tr>
<tr>
<td></td>
<td>Chewing with mouth open: 6%</td>
</tr>
<tr>
<td></td>
<td>Chewing improperly: 6%</td>
</tr>
<tr>
<td></td>
<td>Stuffing: 6%</td>
</tr>
<tr>
<td></td>
<td>No: WNL: 68%</td>
</tr>
<tr>
<td>Preference for a particular food</td>
<td>Yes soft: 2%</td>
</tr>
<tr>
<td></td>
<td>Sweet: 15%, sticky: 6%</td>
</tr>
<tr>
<td></td>
<td>Sour: 3%, No preference 56%</td>
</tr>
<tr>
<td>Reluctance to try new food</td>
<td>Yes 53% No: 47%</td>
</tr>
<tr>
<td>Need additional oral hygiene instruction</td>
<td>Yes 38% No: 62%</td>
</tr>
<tr>
<td>Need for dietary counseling</td>
<td>Yes 9% No 91%</td>
</tr>
</tbody>
</table>

In Klein and Nowak's study, they reported a normal eating pattern of 68% of their autistic subjects with 14% pouching, 6% chewing with mouth open, 6% eating improperly, and 6% stuffing. Hence, there was only a small portion who pouch their food. Many of the parents were involved with the patients' oral hygiene. Only 12%
needed no help and the majority needed total or some assistance from the parents (88%). But then more than one-third of the parents was interested in additional oral hygiene instructions. So that means even there was a majority of parents who took care of their children’s oral hygiene, many of them were not particularly interested in their brushing and flossing habits.

With regard to oral hygiene practice, Lowe and Lindermann (1985) commented that the oral hygiene status of the autistic patients were lower than the non-autistic. This was because autistic patients did not have the manual dexterity required for toothbrushing and they do not comprehend the importance of oral hygiene. Those who were younger and non-institutionized had better oral hygiene status than the older and the institutionized autistic subjects. This was simply because those who lived at home have their parents brushed their teeth and younger autistics were easier to manage than those who were older and have bigger body sizes. Consequently, the parental involvement in providing oral hygiene is important such that more emphasis on training should be placed on training the parents to keep up their children’s oral hygiene up to an acceptable level.

6.2.4 Orthodontic anomalies

Malocclusion generally occurs in children between the age 7 and 12 (Vittek et al., 1994). The anomalies are primarily caused by genetics with a number of controls like nutrition, caries susceptibility, development of masticatory apparatus, and the growth and development of the upper face. Vittek and co-workers (1994) suggested chromosomal abnormalities such as Down syndrome cause poor growth and development of the upper face; twenty one facial distortions have been known to
associate with mental impairment. In addition, Vittek and co-workers (1994) performed a comparison of the incidence of various orthodontics anomalies with respect to Angle classes, crowding, crossbite, openbite, and overjet with various mental disorders including seizure disorder, cerebral palsy, autism, and Down syndrome. Their results are in table 6-2.

Vittek and co-workers (1994) compared the occurrence of orthodontic anomalies in 458 persons with various degree of mental impairment (MR). Among these 458 mentally impaired persons, 26 of them were diagnosed to have autism. Approximately 75% of all autistic patients are mentally impaired throughout life (Davila, 1988). When the severity of malocclusions were compared with the level of mental impairment, they found the more severe malocclusions in the moderately and severely mentally

Table 6-2. Percent incidence of orthodontic anomalies in 458 mentally retarded developmental disabled persons with various medical diagnosis (Vittek et al., 1994).

<table>
<thead>
<tr>
<th>Anomaly</th>
<th>Healthy USA N=8841</th>
<th>Organic brain syn N=238</th>
<th>Seizure disorder N=90</th>
<th>Cerebral palsy N=47</th>
<th>Autism N=26</th>
<th>Down syn N=57</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angle class</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>75.0</td>
<td>71.6</td>
<td>78.5</td>
<td>52.0</td>
<td>25.0</td>
<td>53.7</td>
</tr>
<tr>
<td>II</td>
<td>20.0</td>
<td>16.9</td>
<td>13.1</td>
<td>38.8</td>
<td>56.3</td>
<td>9.8</td>
</tr>
<tr>
<td>III</td>
<td>5.0</td>
<td>11.5</td>
<td>8.4</td>
<td>9.2</td>
<td>18.8</td>
<td>36.5</td>
</tr>
<tr>
<td>Crowding</td>
<td>NA</td>
<td>1.3</td>
<td>4.7</td>
<td>6.9</td>
<td>6.3</td>
<td>9.8</td>
</tr>
<tr>
<td>Crossbite</td>
<td>1.4</td>
<td>20.8</td>
<td>13.1</td>
<td>15.5</td>
<td>25.0</td>
<td>14.6</td>
</tr>
<tr>
<td>Open bite</td>
<td>2.4</td>
<td>10.6</td>
<td>9.3</td>
<td>13.8</td>
<td>12.5</td>
<td>4.9</td>
</tr>
<tr>
<td>Overbite</td>
<td>8.5</td>
<td>6.8</td>
<td>12.1</td>
<td>5.2</td>
<td>6.3</td>
<td>7.3</td>
</tr>
<tr>
<td>Overjet</td>
<td>9.6</td>
<td>10.6</td>
<td>13.1</td>
<td>22.4</td>
<td>31.3</td>
<td>7.3</td>
</tr>
<tr>
<td>Definitive Orthodontic Anomalies(%)</td>
<td>37</td>
<td>50</td>
<td>61</td>
<td>92</td>
<td>99</td>
<td>82</td>
</tr>
</tbody>
</table>
impaired patients (Vittek et al., 1994). They reported that 21.8% of the mildly impaired had Angle Class II and III malocclusion whereas there were 27.8% of the moderately to severely mentally impaired had Class II and 31.8% of them had Class III malocclusion. Furthermore, they noted a 2 to 3 times higher occurrence of openbite and overjet in the moderately impaired group than other two groups. However, crossbite and overbite were notably lower in the moderately and severely mental impaired groups than in the mildly impaired group. When the comparisons were divided into separate mental diagnoses as in table 6-2, the autistic group was shown to have higher malocclusion rates than the healthy group with respect to Class II and III malocclusion, crossbite, openbite, and overjet. Overall, about 99% of all the subjects with autism had definite orthodontic anomalies at the time of the investigation. Vittek and co-workers (1994) concluded that the severity of mental status was correlated with the increased incidence of both acquired and hereditary orthodontic anomalies.

6.3 PATIENT MANAGEMENT OF AUTISTIC PATIENTS FROM THE DENTIST’S POINT OF VIEW

Both Kopel (1977) and Lowe and Lindermann (1985) stated that the dental characteristics of autistic patients when compared with the general population were somewhat “remarkable.” Patient management of these patients, especially in the dental office, poses some special challenges and difficulties to the dental personnel. First, the autistic patient “is inherently unresponsive to demonstrations and will resist any effort to establish personal contacts with the dental personnel (p.58)” (Davila and
Jensen, 1988). Second, their unique feature of repetitiveness makes it especially
difficult for dental personnel to “tell-show-do” dental instruments and procedures.
Swallow (1969) indicated that the treatment of autistic patients can be very exhausting
for dentists. Lowe and Lindermann (1985) described that two major problems of
autistic children being treated in the dental office are their lack of cooperation, and
inappropriate patient/dentist interaction.

6.3.1. A case report from Davila and Jensen (1988)

Davila reported a 10 years longitudinal report of delivering dental care to an
autistic patient in Monroe Developmental Center in Rochester, New York. The
chronological sequence of the 8 year treatment is summarized in table 6-3.
<table>
<thead>
<tr>
<th>Patient's age</th>
<th>Method of sedation</th>
<th>Dental outcome</th>
<th>Comments from dental record</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 3/12</td>
<td>Meperidine HCl 50 mg Promethazine HCl 25 mg Scopolamine 0.2 mg administered IM 35 min before app</td>
<td>1</td>
<td>No treatment provided</td>
</tr>
<tr>
<td>8 9/12</td>
<td>Meperidine HCl 75 mg Promethazine HCl 32 mg administered IM 40 min before app</td>
<td>1</td>
<td>No treatment provided</td>
</tr>
<tr>
<td>8 10/12</td>
<td>Meperidine HCl 50 mg Promethazine HCl 25 mg administered IM 30 min before app</td>
<td>2</td>
<td>No treatment provided</td>
</tr>
<tr>
<td>8 10/12</td>
<td>Chloral hydrate 1 g administered orally 35 min before app (dentist unaware of type of medication used)</td>
<td>2</td>
<td>Prophylaxis of aspirant attack</td>
</tr>
<tr>
<td>8 11/12</td>
<td>Meperidine HCl 50 mg Promethazine HCl 25 mg administered IM 40 min before app</td>
<td>2</td>
<td>No treatment provided</td>
</tr>
<tr>
<td>8 11/12</td>
<td>Chloral hydrate 1 g administered orally 45 min before app</td>
<td>2</td>
<td>Full prophylaxis completed</td>
</tr>
<tr>
<td>1 0/12</td>
<td>Chloral hydrate 1 g administered orally</td>
<td>3</td>
<td>No treatment provided</td>
</tr>
<tr>
<td>14 3/12</td>
<td>Chloral hydrate 1.5 g</td>
<td>4</td>
<td>Injection of local anesthetic successful, treatment not completed</td>
</tr>
<tr>
<td>14 6/12</td>
<td>Chloral hydrate 1.5 g</td>
<td>4</td>
<td>Injection of local anesthetic successful, treatment not completed</td>
</tr>
<tr>
<td>15 2/12</td>
<td>Thorazine HCl 200 mg administered orally 60 min before app</td>
<td>5</td>
<td>No treatment provided</td>
</tr>
<tr>
<td>15 5/12</td>
<td>General anesthesia Glycopyrrolate 0.2 IV Thiopental sodium 250 mg N₂O₅ = eutectane Succ. chloroform 40 mg</td>
<td>3</td>
<td>Resection of 32 tooth surface, full mouth prophylaxis</td>
</tr>
<tr>
<td>16 8/12</td>
<td>General anesthesia Ketamine HCl 200 mg IM Thiopental sodium 350 mg Lidocaine N₂O₅ Succ. chloroform 50 mg</td>
<td>3</td>
<td>Full mouth prophylaxis, restoration of fractured tooth and treatment of recurrent decay in one tooth</td>
</tr>
</tbody>
</table>

As illustrated in table 6-3, the dentists had administered various combinations and doses of sedative agents just to achieve enough cooperation for the dentists to complete an oral examination and a prophylaxis. The sedative medications that were used during this 8 year-long period were meperidine, promethazine, chloral hydrate, diazepam, thiordazine, and thorazine. Eventually, the dentists had to put him under general anesthesia in the operating theater to complete the necessary dental procedures. Davila and Jensen concluded in their paper that autistic patients were very difficult to manage, and they were not able not able to design a predicable cocktail.
sedation programme. They indicated the use of general anesthesia, with the associated risks and costs, were the solution to the patient’s long term dental problems.

6.3.2 Pharmacological management techniques

Several investigators (Braff and Neelson, 1979; Karnen, 1985; Kopel, 1985; Davila and Jensen, 1988) advocated the use of pharmacological agents in the dental management of autistic patients. Some common medications were nitrous-oxide, diazepam, hydroxyzine, chloral hydrate, diphenhydramine, and meperidine. They had been studied for their effects in various dosages and combinations. The overall success rates ranged from limited (Kopel, 1985; Davila and Jensen, 1988) to 70% success (Braff and Neelson, 1979). Nevertheless, both Karnen and Skier (1985), and Davila and Jensen (1988) groups commented that any success with sedative techniques was considered unpredictable.

6.3.3 Behavioral management methods

Loe and Lindermann (1985) stress that the role of establishing communication between a dentist and the autistic patient is an utmost important step in successful treatment. However, the communication between the dentist and the patient is hindered by the autistic’s impairment. Thus, the techniques which Klein and Nowak (1998) suggested for behavioral management of autistic children were same as those for non-autistic children. They were tell-show-do, immediate and frequent positive and negative reinforcement, immediate verbal praise and short simple oral commands.

The use of augmentative communication techniques that have been commonly used among the deaf have been recommended (Sheehy et al., 1993). Such
communication method has been developed to compensate for impairment and
disability of non-speaking individuals through the use of special augmentative
components like special gestures, graphic symbols, communicative aids, signs and
others. Sheehy et al. (1993) stated that children with communication impairment such
as cerebral palsy, mental impairment, and autism may benefit from such techniques in
the dental environment. Since the mid-1970’s, speech-language pathologists have
accepted the use of a communication board for non-speaking individuals. The use of a
visual board (figure 6-2) allows non-speaking individuals to communicate by pointing
directly at the symbols or words with their hands, eye gaze, special pointers, or light
sources.

A communication board for the dental setting is a cardboard with iconic picture
displays which is designed to serve the dental environment and the patient’s needs
(figure 6-2, table 6-4). Such a cardboard is for non-speaking children like those with
autism with adequate cognitive ability, good pointing skills, and personal acceptance.
If the autistic child has limited ability to use finger pointing, the occupational or
physical therapists will need to design some alternative methods for their access. The
team members, which include a dentist, speech therapist, physical therapist, will need
to give the patient time to practice and to provide adequate training prior the use of
the communication board in the dental setting. However, a major drawback is that
severely autistic children may not have the cognitive ability to comprehend the
symbols. Furthermore, the autistic user is assumed to adopt a passive role and to be
responsive to, and controlled by the therapist.
Figure 6-3. A sample communicative board for use in the pediatric dental setting (Sheehy et al., 1993).

<table>
<thead>
<tr>
<th>Dental Terminology</th>
<th>Word substitute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophy angle &amp; rubber cup</td>
<td>Electric &quot;toothbrush&quot;</td>
</tr>
<tr>
<td>Radiograph</td>
<td>Picture</td>
</tr>
<tr>
<td>Anesthetic</td>
<td>Sweet juice</td>
</tr>
<tr>
<td>Rubber cam</td>
<td>Raincoat</td>
</tr>
<tr>
<td>Rubber cam clamp</td>
<td>Button</td>
</tr>
<tr>
<td>Amalgam filling</td>
<td>Silver star</td>
</tr>
<tr>
<td>Fissure sealant</td>
<td>Like &quot;paint polish&quot; your teeth</td>
</tr>
<tr>
<td>Air</td>
<td>Wind(y)</td>
</tr>
<tr>
<td>Salivary ejector</td>
<td>Straw</td>
</tr>
</tbody>
</table>

Table 6-5. Explanation of some pictures and word symbols for figure 6-3.
Backmann and Pilebro (1999) attempted a novel strategy called "visual pedagogy" for autistic children, which was based on an educational concept named TEACCH model. TEACCH stands for Treatment and Education of Autistic and related Communication Handicapped Children. Under this model, autistic children are viewed to react more favourably to structured situations than to unstructured situations. Most autistic children have impaired cognitive abilities and the child is told what to do, where, when and how with some pictures which are schematically designed. Furthermore, the two investigators believed children with autism were easier to communicate with using pictures than with verbal words.

The primary requirement of this strategy is that the child with autism always has to meet the same dental personnel in the same dental surroundings. A pictorial book (figure 6-4) with colour-prints was produced the visual description of every step of the dental treatment. For example, the front door of the dental building, the waiting room, the dentist, the operating room and the instruments that the child will encounter. Each time the parent should show one or two pictures and cover the remaining pictures to avoid distracting the child with unnecessary information. Before the treatment begins, the dentist has to meet the parents and be given relevant information about the child such as the child’s phobia, ways to communicate, rewarding strategies, general health, medication, and experience on dental care. At home, the parent and child have to prepare for the dental visit by reading the picture book together (Backmann and Pilebro, 1999).
Figure 6-4. Examples of sequences of pictures showing the milieu in the clinic, the dentist, illustration if “mouth wide open” instruments and objects to be used. Pictures irrelevant for the actual treatment session are covered with blank paper (Backmann and Pilebro, 1999)
Then in the dental office, the dentist’s conversation with the child is limited to some simple and concrete statements, which the parents were taught to teach their child previously from the book reading. Backmann and Pilebro (1999) carried out this project on 16 autistic children, 15 boys and 1 girl for 1.5 years. The cooperation of the children was compared with 16 other children who had autism but not treated with the visual pedagogy. Their results are listed in table 6-6.

Table 6-6. Results after 1.5 yr applying visual pedagogy in dentistry (Backmann and Pilebro, 1999)

<table>
<thead>
<tr>
<th>Activity</th>
<th>Uncooperative</th>
<th>Reluctant</th>
<th>Cooperative</th>
<th>Not tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entering the dental surgery</td>
<td>16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitting/lying in the dental chair</td>
<td>16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouth wide open/showing the teeth</td>
<td>15</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toothbrushing</td>
<td></td>
<td>10</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Examination with mirror</td>
<td>1</td>
<td>10</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Examination with probe</td>
<td>1</td>
<td>11</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Fluoride varnish</td>
<td>3</td>
<td>2</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Tooth-cleaning with prophylactic paste</td>
<td>1</td>
<td>4</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>X-ray exam</td>
<td></td>
<td></td>
<td>2</td>
<td>14</td>
</tr>
</tbody>
</table>

All sixteen autistic children showed full-cooperation on entering the dental surgery, sitting on the dental chair, and opening their mouth wide-open/showing the teeth except one child. Fourteen children showed cooperation in oral examination with mirrors while only 10 to 11 children showed cooperative behaviour in toothbrushing and oral examination with probes. Only 2 children showed cooperation in more complicated procedures like fluoride varnish, application and radiographic exam. Meanwhile, four showed full-cooperative behaviour in tooth cleaning with prophylactic paste. Each visit took about 15-20 min and broken appointments were rare. They concluded that the visual pedagogy technique in the dental environment was successful such that the autistic children had developed cooperation beyond the expectation of the parents. They concluded that the use of visual pedagogy was a way
to introduce dentistry and to provide the possibility of preventive density to autistic children. These children overall develop superior cooperation throughout the study period.

Burkhard (1985) indicates the use of behavioural modification such as positive reinforcement, operant conditioning, modeling, and desensitization may be beneficial in structuring a dental visit. Such procedures are treatment of choice in dealing with autistic children but the professional must be knowledgeable about the procedures and have a lot of patience. There are eight steps in the behavioural modification (Drash, 1974).

(1) Put the child at ease on the first visit through the extensive use of positive social reinforcement.

(2) Explain to the autistic child about the simple reward system with concrete language that have been discussed with the parents.

(3) Provide constant social reinforcement (rewards) throughout the session.

(4) Provide verbal praise immediately and very precisely following each bit of desired behaviour.

(5) Provide points verbally each time a desired behaviour occurs.

(6) Avoid talking about the procedure during treatment.

(7) Be sure the points will entitle the child to receive a prize at the end of the treatment session.

(8) End each treatment session with lavish praise for the child’s good behaviour.

Burkhard (1985) also suggested some special modes of language restructuring, minimal body movement, and background music to facilitate the delivery
of dental care to autistic children. He states that the dentist should use short, simple, ambiguous sentences because autistic children generally lack the basic language development in order to understand long and complex sentences. Also, the dental professional should not use any slang, or metaphor to confuse autistic patients because they don't have the language cognitive capacity to understand any figurative speech. The operator should let the child know what exactly is taking place in his/her surroundings such as "the sound you are hearing is water being poured into a cup (p62)" (Burkhard, 1984). Harris (1978) indicated that autistics have trouble organizing their thoughts and behaviours. Harris suggested when the children were advised what not to do, they had equally had to be told what they ought to do. For instance, the dentist may comment on the autistic's self-injurious behaviour in the office, "I know you are anxious, but you do not have to bite your hand. You may squeeze them together instead" (Harris, 1978). Dentists should have minimal bodily movement during the dental procedure because autistic children are easily distracted (Kopel, 1977). Kopel also stated that autistic children appear to have a high degree of lateral vision; hence, any movement laterally to the child has been proved distractive. Autistic children, furthermore, seem to react positively with music (Burkhard, 1988); consequently, some music in the dental office may enhance good behaviour in these children.

6.3.4 Reducing fear in children with autism

Autistic children are often unable to cooperate with dentists because of their fear of the dental environment. According to Luscre and Center (1996), these children were fearful of the sight and sounds in the dental operatory. Autistic children are often disturbed by dental treatment and most dentists cannot deal with the stress of treating
these children (Kopol, 1977). Their dental needs are often neglected or delayed to a point that the caries becomes so severe that requires hospitalization and treatment under general anesthesia. The two researchers, Luscre and Center, described a method, which consists of desensitization, symbolic modeling, and positive reinforcement to reduce the fear of these autistic children.

Luscre and Center (1996) divided a dental examination into 13 small steps in the hierarchy of increasing difficulty (table 6-7).

Table 6-7. Steps in the Hierarchy of a Dental Examination (Luscre and Center, 1996)

1. Leave car/classroom
2. Enter building/hall
3. Enter waiting room
4. Sit/play in waiting room
5. Enter dental operatory
6. Sit in dental chair
7. Lean back in chair
8. Wear apron
9. Tolerate light
10. Open mouth for mirror
11. Open mouth for explorer
12. Open mouth for evacuator
13. Tolerate dentist/novel adult during exam

Each subject went through an average of 20 in-office sessions and 4 video sessions. During each session, the operator showed a video of a dentist and a normal child modeling the steps in the coping hierarchy. They reported one out of three subjects was able to tolerate a full dental examination after 16 sessions while the other two could tolerate a partial oral examination. The two researchers rated the result “good” such that these autistic children were trained to have reduced fear at the dental environment and show some to full cooperation to an upsetting, fear-provoking experience, such as a dental examination.
6.3.5 Kopel’s (1977) desensitizing method

Kopel (1977) suggested a behavioural management method in the dental setting which involved a time consuming progression of conditioning and reinforcement with simple demonstrations along with intermittent positive rewards and the termination at the right time. The management must be in small progressive steps because the oral cavity, to these autistic children, is a zone of great psychological importance and gratification. In the mind of an autistic child, dental treatment may actually be a threat to a private area rather than a necessity.

Kopel (1977) illustrated his idea of desensitization with a case example in which he suggests the behavioural therapy should start with a simple rehearsal procedure in which parents were taught to practice some simple oral hygiene procedures at home after a brief initial appointment with a partial oral examination. He advises the dentist to give the parent a dental mirror, a prophylaxis cup, a small amount of prophylaxis paste, and some x-ray films. When the parent rehearses with these props at home, he/she should conduct with simple concrete commands like “hands down,” and “look at me.” In the subsequent dental appointments, as the child has become familiar to these props, the dentist should be able to conduct some simple dental procedures. Kopel (1977) also emphasized the use of desensitization along with a great deal of positive reinforcement. When the child cooperates in each step of the dental appointment, the dentist should reward the child with a verbal praise, an affectionate touch, or a taste of a desirable food; it was also suggested that honey, peanut butter, or Cheerios could serve as reward items (Kopel, 1977). In short, behavioural therapy with some positive reinforcement may teach autistic children to become cooperative in a dental environment.
6.4 SELF-INJURIOUS BEHAVIOUR (SIB)

Self-injurious behaviour (SIB) is one of the most distressing events to the families of children with mental impairment (Howlin, 1993). SIB may range from self-pinching, scratching to severe self-biting, or head-banging (Klein and Nowak, 1998). Self-mutilation of the oral structures has been reported associating with autism (Johnson et al., 1996) and its prevalence is about 4-5% of the affected population (Klein and Nowak, 1998). Johnson and co-workers (1996) state that self-injury was a maladaptive means of seeking social attention. If the SIB is primarily attention seeking, ignoring the behaviour will cause a decline in the child’s frequency. This is called an “extinction procedure.” Nevertheless, it may take up to several thousand responses to see some positive effects with such a technique. This may only be tolerable if the maladaptive behaviour is relatively mild and is certainly not feasible for more serious self-inflicted injurious.

6.4.1 Case reports

Johnson and co-workers (1996) reported a case that a 35 year-old autistic man developed a deep gingival cleft (figure 6-5) below his lower left canine. During the clinical exam, the patient showed repeatedly the scratching of the affected area with his fingernail. The clinical feature resembled a variety of gingival diseases like inflammatory
hyperplasia, periodontal disease, and factitious stomatitis. Recommended by the
psychiatrist, the dentist attempted to use a simple task-reward system on top of the
behavioural modification for his abnormal behaviour that included hostility to the
parent, and scraping the gingiva. The dentist agreed to give the child baseball game
tickets if he modified his behaviour and used the chlorhexidine mouthrinse as
prescribed to control his oral hygiene (Johnson et al., 1996).

The patient was examined 4 weeks later and the hyperplasia along with
gingivitis had resolved. Then at a three month review, the previously lacerated gingiva
had healed with satisfactory results. However, when the dentist arranged to give the
patient the promised baseball game tickets, the game was cancelled due to a contract
dispute. The patient then resumed the gingival self-injurious habit shortly after the
announcement of the contract dispute. Johnson et al. (1996) concluded that the
behavioural therapy had achieved its initial success despite the unforeseen accident of
not able to provide the promised reward.
Johnson and co-workers (1996) discussed the diagnosis of SIB was difficult because it resembles other diseases like focal inflammatory hyperplasia, periodontal disease, autoimmune mucosal disorder, traumatic eosinophilic granuloma, traumatic ulcerative granuloma, and factitious injury. Steward and Kevnohan (1972) defined self-inflicted injuries with the following criteria:

(1) Simple or multiple focal lesions.

(2) Lesions that fail to correspond to known diseases.

(3) The area is easily reached by the patient.

(4) Abnormal tissue outline with bizarre shape and contour.

Some reported cases of self-injury in the oral region are autoextraction, ulceration, puncture wounds, biting of the tongue, cheek and lips (Pattison 1983, Heasman et al., 1994; Mass and Gadoth, 1994; Smith et al., 1994).

Polyzois (1989) reported a similar case of self-injury of an autistic boy and described how he stopped the behaviour with the use of a custom mouth protector and behavioural therapy as a collaborating effort with a psychologist. He described a 10 year-old boy with autism who was presented with a lacerated lower lip and tongue. The lower lip and tongue were so severely lacerated that they were covered by pseudomembrane at the time of the oral examination. The treatment consisted of desensitization, positive reinforcement (rewards), and the fabrication of a set of mouth protectors. The child was familiarized initially with impression trays, impression taking procedures, and a set of mouth protectors along with positive and enthusiastic reinforcement. Positive reinforcement was in the form of rewards with verbal praises,
affectionate touches, and colourful objects. The mouth protectors were designed to cover the palate, and teeth deep into the depth of the lingual, buccal, and labial vestibules. The mouth protector (figure 6-6) served as a restraining device to allow the healing of the tongue and lower lip while the child was being treated for his self-mutilation with intensive behaviour therapy. Polyzois (1989) concluded that the use of the silicone custom mouth protector combined with the behavioural modification therapy could aid in reducing the child's self-injurious behaviour of the oral cavity.

Figure 6-6. Silicon custom mouth protectors (Polyzois, 1989)

6.5 THE ANAESTHETIC MANAGEMENT OF AUTISTIC CHILDREN

Most children can be successfully managed and treated in the dental office; however, there is a group of paediatric patients, like those who are mentally impaired or physically disabled, who require dental treatment under general anaesthesia (Bohaty and Spencer, 1992). Autistic children are considered to be special care patients and they may require the use of general anaesthesia for necessary dental treatment.

6.5.1 Why should autistic children be treated under general anaesthesia (GA)?

Hulland and Sigal (2000) performed an investigation on 1384 patients who were registered with some forms of disabilities in a hospital. They determined a set of
selection criteria that could identify patients who were likely candidates to be treated with general anaesthesia in the hospital setting. The most prevalent profile traits, identified in decreasing order as predictors for those who need dental care under GA were:

1) Behavioural problems-moderate to severe.
2) Mental impairment- moderate to severe.
3) Seizure disorder- particular uncontrolled.
4) Scoliosis.
5) Autism.
6) Limited dental procedures in the dental clinic.
7) Taking seizure medication on a regular basis.
8) Regular use of psychotropic drugs.

Among these factors, the criterion of behavioural factors seems to be the strongest predictor. Even though autism was ranked as a somewhat important (6th) predictor for treatment under GA, a number of autistics do demonstrate moderate to severe behavioural problems like unresponsiveness, resistance of personal contact (Davila and Jensen, 1988), total lack of cooperation (Rainey and Walt, 1998), and hostility (Johnson et al., 1996). The relation between autism and behavioural problems were apparent; Hulland and Sigal (2000) identified 31.9% of autistic children among his subjects had moderately behavioural problems, and 17.4% of them had severely behavioural problems. Furthermore, approximately 75% of all patients with autism are mentally impaired throughout life (Davila and Jensen, 1989). Children with autism, thus, fit the two most important predictors for Hulland and Sigal’s list of GA criteria (Hullard and Sigal, 2000). Therefore, unmanageable autistic children with autism appear to benefit greatly from comprehensive dental care which includes the
necessary preventive, restorative and surgical treatment at one appointment under general anaesthesia.

6.5.2 Research data on the use of general anaesthesia on dental patients with developmental disability

Several investigators have conducted questionnaire surveys regarding the provision of dental treatment under general anaesthesia in patients with autistic disorder. Klein and Nowak (1999) found that 37% of their 43 autistic subjects needed comprehensive or difficult dental treatment to be carried out under general anaesthesia in the operating room. Hulland and Sigal (2000), likewise, reported that 65.2% of their autistic patients among the 1384 subjects required dental treatment under GA. Ananthanarayan and co-workers (1998) identified that autism was ranked the 6th most common developmental disability among others like seizure disorder, Down syndrome, and cerebral palsy which all require the use of general anaesthesia for dental treatment because such impairments had high incidence of poor cooperation and aggressive antagonist behaviour.
6.6 CONCLUSIONS

- Research has shown that autistic children have a low incidence of dental caries but a high incidence of gingival disease.

- Autistic children and adolescents generally have low oral hygiene status due to their limited manual dexterity and their inability to comprehend the importance of oral hygiene.

- Most autistic children and adolescents exhibit atypical oral habits and food preferences.

- The majority of autistic children and adolescents have definite malocclusion that require orthodontic intervention.

- Autistic children and adolescents are uncooperative in the dental office. Dentists have to use various pharmacological agents and behavioural modification in order to complete the necessary dental procedures. Among all the management methods available, the use of general anaesthesia is still the best method even with its associated risks and cost.
Chapter 7 Some final words

In the movie *Rainman*, played by Oscar winners Dustin Hoffman, and Tom Cruise, Charlie (Cruise) uncovers a surprise that his Dad’s inheritance has been left to his autistic savant brother, Raymond (Hoffman). Determined to extort his fair share of the money, Charlie abducts his older brother and holds him hostage. On their way driving from Cincinnati to Los Angeles, he begins to understand about Raymond’s narrow world. When he first visits the group home where Raymond has lived for 20 years and is disappointed by his brother’s eccentric behaviour, the psychiatrist explains

[that he is an]...autistic savant with certain abilities and certain deficiencies.
He is quite high functioning and has disability of his sensory input processes....
He can’t express himself or probably understands his emotion in a traditional way.
There are dangers everywhere for him, routines, rituals and he has to protect himself.
He has the way he asks, sleeps, eats, goes to the bathroom, talks...any break from his rituals can get terrifying...

The psychiatrist’s explanation to Charlie illustrates some very typical features of autistic patients such as repetitiveness, stereotypic behaviour, and inability to communicate.

Like Raymond, most autistic patients remain institutionized for life. Even though medical scientists have been looking for some miracle drugs to treat autism; most pharmacological treatment for the last 40 years has had limited success. However, through intensive behavioural modification and training, most autistics can have normal lives and can carry out daily routine activities such as eating, toothbrushing,
and bathing.

In this 1989 popular Hollywood film, *Rainman* gives the first time an insight into the mind of an autistic person. The adult Raymond whom was nicknamed by his younger brother as “rainman” was based on some real cases and one of them was actually from Kanner’s original documentation (Houston and Frith, 2000). Typical autistic behaviour, mannerism, and special interested are represented faithfully in the film such that the public has a more understanding of autistic people. Likewise, in my dissertation, I have attempted to look into the aetiology of autism from the standpoint of human biology and genetics; in addition, I have presented some treatment modalities for autistic patients from the perspective of modern medicine, psychology, and also dentistry. I hope this dissertation will serve as a future reference for dentists and other health professionals, and perhaps raise the public awareness of autism.
REFERENCES


