Article *NIMHANS Journal*

Biological Factors in Childhood Autism

Volume: 07 Issue: 01 January 1989 Page: 91-101

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In defining the syndrome of early infantile autism almost forty years ago Kanner appeared to opt for psychodynamic etiology although paradoxically at the same time stressing that the disorder was 'inborn' [1]. On the basis of his observation of the parents of autistic children, Kanner believed that they were 'refrigerator' type parents; cold, intellectual, obsessive, highly educated people who had been unable to form the normal bonds of attachment with their child. This speculation unfortunately led to much distress amongst parents of autistic children. Happily, little credence is given these days to this proposition. A number of studies have supported the counter claim, where it is found that a majority of parents of autistic children and intelligent and highly educated (and this has indeed been the case in a number of studies) [2], [3]; this has most likely been the result of referral artefacts; it is these kinds of parents who persist in consulting professionals until they receive an acceptable diagnosis.

The current consensus of opinion is very much towards a biological basis for childhood autism [4] "Central nervous system pathology" is a phrase often invoked. However, very much more progress has been made in describing and measuring the behavioural deficits in the disorder than in solving the puzzle of its etiology. Clinical observation and experimental research have both indicated that the disorder may be seen as basically a cognitive one; involving not only inability to deal with language and communication processes but at a deeper level including an inability to process information in a meaningful way and to use such information to adapt normally to a complex environment [5], [6]. The weight of the evidence for etiology of Childhood Autism appears to support biological influences although their nature is unclear.

Genetic factors

Because of the rarity of the syndrome, genetic studies are necessarily scant. In addition there are both methodological and interpretative difficulties in searching for genetic factors along with a lack of knowledge of the precise mechanism of genetic transmission and manifestation. One of the arguments which has been proffered as support for the existence of autism as a distinct syndrome which is different from other childhood psychoses has been a genetic one. In relatives of autistic children there is no raised incidence of mental illness, whereas in childhood schizophrenia the strong genetic influence is well documented. Very few autistic adults marry and produce children so that this avenue of exploration of genetic influence is not so far available, although it may perhaps be a possibility in the future. Lotter [7] reported that the rate of autism in siblings of autistic children is 50 times higher than the population risk of approximately 4 per 10,000.

Support for genetic factors is quite strong in the work of Folstein and Rutter [8] in which 21 twin pairs were studied in detail. In the 11 monozygous pairs, 36% were concordant for autism. A significant finding was that 82% were concordant for cognitive disorder; including autism. This compared with a

concordance rate of 0% for autism in the dizygotic pairs and a rate of 10% for cognitive disorder. Cognitive disorder included mental retardation, language disability and educational difficulties. This finding may also be compared with that of Bartak et al [9], where speech delay was noted in a quarter of the families of his sample of autistic children. Folstein and Rutter also found that there was increased biological hazard associated with birth stress in 12 autistic members of the 17 discordant pairs. They argued that genetic factors are important in autism but that what may be inherited is a vulnerability to cognitive/language deficit or abnormality which is expressed in its most sever form in autism. The evidence additionally suggested that brain injury during he perinatal period may be related either to itself or in combination with a genetic predisposition to the development of autism. However as Rutter [10] noted, cytogenic studies provide no evidence that autism is associated with major chromosomal abberations, which means that one can still only speculate concerning the nature of the genetic mechanism which may be involved.

An American study of siblings of autistic children [11] has provided further evidence for the inheritance of congnitive disabilities, including language problems, specific learning difficulties and mental retardation, in a subset of autistic families. They reported a familial incidence rate of such problems of 19.5% compared with 3% in their control sample of families with a Down's proband.

Ritvo and his colleagues [12] have mounted a major study of genetic influence in autism in investigating families with more than one autistic child in the USA, Canada and France. They excluded identical twins from the study but of the 31 sets identified, 30 were considered concordant for autism (although for only 23 sets was diagnosis and zygosity satisfactorily established). Of the 26 sets of dyzygotic twins, tow were concordant for autism.

Classical segregation analyses were used to test hypotheses of autosomal inheritance of autism and to examine the goodness of fit of the polygenic threshold model for 99 children and their 47 families. Results were consistent with autosomal recessive inheritance; the autosomal dominant and polygenic threshold models were not supported. However Ritvo et al [12] noted that fact that the sex ratio in his sample 3:1, which is consistent with other studies [13] and difficult to explain via the autosomal recessive model. He also noted that results from these very singular families may not be generalizable to families with only one autistic child.

Spence reviewed genetic studies in 1976 and concluded that any genetic mechanism would have to be polygenic or multifactorial and that there was a lack of evidence for any specific mechanism for autism. De Myer et al [13] have drawn attention to difficulties with genetic hypotheses in relation to schizophrenia and autism pointing out that concordance rates in MZ twins may be misleading in the absence of information concerning pre-natal environment, particularly the influence of a single chorion in the pre-natal environment.

It appears that a genetic factor or factors may be influential in at least some cases of autism, but that no current evidence it would have to be considered as a general rather than a specific influence. The what and the how of inheritance remains poorly understood. It could not be concluded that the evidence is strong at this stage since it is well known that twins face extra hazards at birth thus complicating the most powerful research paradigm; and the Folstein and Rutter study which provides the clearest information to date was careful to report the raised incidence of perinatal stress in their twin sample. Thus both because of lack of knowledge of genetic transmission processes and the lack of reproduction amongst autistic persons further support for genetic involvement must await the availability of further evidence.

Pre and perinatal factors

An obvious candidate for investigation into causes of autism is the influence of pre and perinatal risk factors. It is well known that internal and external stress during pregnancy, during the birth process, and at the time of birth can produce brain damage which may or may not have long term sequelae. Premature infants and low birth weight infants for example are at risk for congenital damage leading to varying degrees of developmental difficulties. However despite considerable research, no general laws relating pre and prenatal factors to various forms of brain damage (eg. cerebral palsy) are available and many infants survive hazardous conditions of pregnancy and birth apparently unscathed.

In a study notable for its reporting of both retrospective and prospective data. Torrey et al [14] reported significantly more prenatal complications in children who developed autism and childhood psychosis. Midtrimester bleeding seems to be of particular importance in both the retrospective and the prospective studies although the causes of the bleeding were obscure. Pregnancy and/or delivery problems have been reported in studies of Australian, Canadian, American and English autistic children too. Report of peri-natal and post-natal problems including convulsions, febrile illnesses, perinatal apnoea, and jaundice may be found in many studies of this kind. Most authors conclude that such biological factors could be etiologically important in a proportion of cases. There is, in fact, no shortage of studies proposing the etiological significance of birth hazards in sub-groups of autistic children [15], [16].

However, unless detailed and accurate records of these traumatic events are available to researchers in this area conclusions are problematical. Retrospective reporting by parents is notoriously unreliable and must be considered especially suspect when reasons for the severe abnormalities of autism are being sought. Relationships between autism and these risk factors are undoubtedly obtained but they are general and do not illuminate the etiology of the disorder.

Physiological factors

The major areas of research effort in the search for physiological abnormalities in autism have been neurobiological investigations, EEG studies, sleep studies and evoked potential studies. These areas are replete with methodological difficulties. Despite this the importance of neurobiological factors in the etiology of autism is strongly argued.

Neurobiological data

Despite earlier benefits that autistic children were free of overt signs of brain damage (indeed this has been in the past one of the exclusionary criteria for the diagnosis of autism), more recent research concerned with neuro-biological factors has indicated support for biologically based etiology. Kolvin et al [17] concluded that at least half of their cases showed organic signs, whilst DeMyer et al [18] using a weighted scoring system to represent brain of dysfunction found that only 14% of their autistic sample were within one standard deviation of the normal score. Deykin and McMahon [19] found

greatly increased incidence of seizures in autistic children with especially high risk at puberty when approximately one third of the sample experienced seizures. It was commonly assumed in the early stage of the study of autism that most cases showed normal development of motor and perceptuo-motor skills even though they may not always have cooperated sufficiently to be accessible to standard testing. There were few obvious signs of neurodevelopmental abnormalities and the grace and skill of spontaneous movement shown by some children was often commented upon. However systematic testing as opposed to clinical data has indicated that motor milestones are often reported as slow. DeMyer [20] has also claimed that gross motor abilities involving the lower limbs are at a retarded level but less handicapped than fine motor and ball handling skill. She sees autistic children as a neurologically disabled group and has described them as 'dyspraxic'.

We have reported a significant excess of 'soft' signs in a group of Australian autistic children including choreiform movements, balance and coordination problems, fingerthumb opposition, extinction to double simultaneous simulation and speech. There were not impairments of gait or muscle tone. Autistic children were notably poor in imitation ability. These studies add weight to the growing evidence of neuromotor dysfunction in autistic children.

A proportion of reported findings are undoubtedly the result of inclusion of children with a variety of biologically based disorders in which autism is part of the symptomatology, nevertheless there does seem good evidence to support the significance of abnormalities in this area. Damasio and Maurer [21] have emphasized the motor deficits of autistic children and suggested that they may implicate in particular, basal ganglia structures in etiology.

Delayed development of hand preference in autistic children is of a similar order to that reported for retarded children and this has been interpreted as suggestive of neurobiological dysfunction or delay. However, studies of handedness in autistic children are inconclusive for a number of reasons and do not permit any interpretations relating to abnormal brain functioning. Establishment of handedness is a developmentally influenced function being frequently inconsistent until the age of four at least. Mixed handedness is common in autistic children and can be seen as an indicator of development delay.

In all of these studies, measurement techniques have been varied and it is important to note that unfortunately developmental researchers still await more acceptable tools' for reliable neurodevelopmental assessment based on adequate standardized developmental data. Satisfactorily normed and widely accepted tests of systems for assessing neurodevelopmental are still not available and the investigator at the moment must choose from a range of batteries advocated by their creators but not providing the systematic, comparative, age related, basic data which is necessary to identify abnormality.

Minor physical anomalies (MPAs) including high arched palate, and low set ears have been reported in some autistic children [15]. The occurrence of MPAs is considered to indicate other CNS abnormalities which relate to cognitive and or behavioural disorder and thus such signs in autistic children would be considered of etiological significance. However the significance of MPAs is uncertain and any etiological connections should be viewed with caution.

EEG studies

The incidence of reported EEG abnormalities in autistic children ranges from 10% to 83% with an

average of 52% [13]. Despite the unacceptable methodology of the majority of studies producing these estimates [22], the lack of agreement in interpretation, and the considerable technical difficulties encountered in recording with severely disturbed children, Small [23] sees the current evidence in this area as reinforcing claims of CNS impairment. On the basis of a thorough review of psychophysiology in 'Early Onset Psychosis', James and Barry [24] could only conclude that characteristic spontaneous EEG irregularities, indicating some CNS disability may (italics mine) exist'. The question of interpretation of abnormalities as indicating under or over arousal remained unresolved according to their review although maturational factors were seen as influential. Evidence related to cardiovascular, respiratory, and electrodermal activity was similarly inconsistent and inconclusive.

On the basis of this research it must be concluded that there, are no EEG abnormalities which are unique to autism despite the studies which report differences between autistic and other groups. There is minimal evidence concerning localization of any EEG abnormalities; they are most commonly diffusely distributed [25]. A general disturbance is thus indicated which does not permit conclusions relating to autism.

Similarly, researchers have reported sleep studies [26] which suggest immaturity in REM sleep but no unique abnormality. Findings of maturational differences in brain mechanism relating to REM sleep should not be surprising when it is recalled that most autistic children are very delayed developmentally and function at an immature level.

Evoked potential data

Brainstem dysfunction in autistic children has been explored using brainstem auditory evoked potentials (BAEPs). Whether the reported abnormal BAEPs result from structural defects of functional impairment is a matter for further examination as is the origin, or source of the abnormalities. Early damage to brainstem structures such as the reticular formation and the inferior colliculi however, could be a consequence of perinatal problems which are sometimes found in cases of autism and could produce the brainstem abnormalities reported by these workers.

A number of researchers have postulated specific brainstem abnormalities as basic to autism eg. the reticular formation; the vestibular system, a dorsal brainstem lesion around the nucleus of the tractus solitarious; a specific lesion in the inferior colliculi, and "neurological dysfunction in the auditory system at the brainstem level". Empirical data to support these hypotheses have not been forthcoming. Tanguay et al [27] (1982) have proposed a relationship between abnormal auditory processing deficits in some children, and the maldevelopment of neural substrates at critical early periods.

Hearing loss has sometimes been identified in auditory evoked response studies suggesting need for care in screening subjects. Attentional problems which characterize autistic as well as other deviant groups of children are clearly very pertinent in evoked response studies and the effects of attentional and maturational factors needs to be established for various groups, before interpretations of data from autistic children can be of more heuristic value. So far findings in these studies suggest immaturity but nothing specific to autism.

Biochemical factors

Despite a considerable number of biochemical investigations there is little data offering enlightenment in this area. Because of the equivocality of organic signs in the majority of cases of autism, biochemical or functional abnormality would seem an obvious target for research. However a review of findings so far does not permit one to relate autism to specific biochemical dysfunctions. Most of the biochemical research too suffers from a number of methodological problems which make the low replication of findings rate almost inevitable. Samples of autistic/psychotic/schizophrenic children in these investigations have often been ill-defined and heterogeneous. Since most of such children are retarded it is essential to control for this factor in comparative biochemical studies, but in fact this is frequently considered (eg. Coleman 1976). Furthermore, methods in biochemical research are many and various and failure to report consistent findings is the inevitable outcome of such variation in experimental techniques. Failure to control for diet and activity factors in subjects, represents an additional point of criticism in the biochemical area.

Catecholamine studies have yielded contradictory findings although there is some suggestion that the catecholamine and indoeamine systems may be implicated in schizophrenia, it is unclear how the abnormalities described relate to autism.

CNS serotonin function has been a prime target for investigators in the biochemical area because of the theory that abnormalities of serotonin metabolism are related to psychotic disorders, and there has been a significant body of research here.

Hyperserotonemia has been reported in approximately one third of autistic children but is similarly found in many medical and neuropsychiatric disorders. Its relationship to any symptom or behaviour is uncertain. There is also the possible influence of developmental delay in general, in affecting slow maturation of systems and there is minimal data to assist the assessment of this factor.

Porges [28] had discussed some of the problems in serotonin research noting that serotonin levels in the blood may not be the same as those in the brain where presumably they are exerting the kind of effects we wish to assess. He has suggested that measurement of platelet serotonin activity may not be a valid biochemical index in autism. Further, although high levels of serotonin are associated with hyporeactivity, autistic children have been shown to be both underresponsive and overresponsive depending on the situation and/or the modality providing stimulation. Clearly there are major problems of interpretation in this research area. De Myer [13] have concluded that 'the most compelling evidence supports the idea that blood serotonin levels are more strongly related to intellectual status than to psychiatric diagnosis' (p415).

Bufontenin in the urine of autistic children and of their parents has been reported [29]. However again no satisfactory interpretation of the finding has been offered. It appears that little specific to autism can be gleaned from these biochemical studies although the relationship between specific psychotic symptoms and biochemical deviance may be worth further exploration.

Enzyme studies have largely produced negative findings as have exploration of zinc, copper and amino acid levels in the blood of autistic children. Neuro-endocrinological studies, immunological studies have also produced some evidence for non-specific abnormalities but no coherent pattern related to a diagnosis of autism.

Autism associated with other disorders Rubella autism

Studies of rubella autism [30], [31] indicate the notable relationship between the two disorders. The incidence of autism in rubella children is much in excess of that in the normal population (412 in 10,000 vs 2-4 cases per 10,000) suggesting a specific link between the rubella virus and the development of autism. Chess [30] has suggested that autism may be one consequence of the invasion of the central nervous system by the rubella virus. She concluded that autism was probably caused by the action of the virus itself, in the same way as autistic behavioural disturbance can be produced by viral encephalitis.

Thus it appears that one of the possible causes of autism may be a viral infection either early in life, or, as an effect later in development of a 'slow virus'. It is known that the rubella virus continues to exerts its effect even up to the age of 2 years. This postulation may be helpful in explaining variations in the severity of autism and mental retardation and in allowing for some variation in age of onset. However, it should be noted that any form of brain damage such as that produced by the rubella virus is likely to increase the risk of the development of behavioural and cognitive handicaps such as those found in autism.

Autism or autistic behaviour is also associated with some other organically based disorders involving retardation. Three disorders particularly appear to produce autistic symptoms with notable frequency although the exact prevalence is unknown; tuberous sclerosis, phenylketonuria and encephalitis. Autism has also been associated with celia disease, congenital syphillis, histidinemia, toxoplasmosis, purine disorder, infantile spasms, Cornelia de Lange syndrome, cytomegalic inclusion disease, neurofibromatosis [32] and the fragile-X syndrome [33]. However the association may be between retardation and autism rather than any relationship with specific syndromes.

Study of the symptoms associated with these disorders serve to illustrate the fact that autistic behaviour can be a consequence of various kinds of insults to the nervous system as well as developing without apparent organic origin.

Autopsy findings

Not surprisingly there are few reports of autopsy findings with autistic children since the disorder is very rare and relatively recently identified, and there is no evidence that autistic children have a lowered life expectancy unless their disorder is complicated by organic disease.

Because of the very mixed samples of cases studies and the inclusion of individuals with clearly organic pathology no conclusions may be drawn from autopsy data.

Computerized axial tomography

There have been several recent studies in which computerized axial tomography has been used to look for structural malformation in the brains of autistic children. Tomography is an X-ray examination technique in which the X-ray tube is moved during exposure so that only structures in a selected plane of the body cast clear shadows. Several different slices of the brain are scanned and the resulting pictures are presented on film permitting assessment of lesion site and extent, analysis of the size and

shape of the ventricular system and of skull and brain asymmetries.

The largest group of autistic children (diagnosed according to DSM III criteria) for whom CAT scan data is available is that studied by Campbell et al [34]. Eleven of their 45 cases showed some ventricular enlargement, however 75% of the sample showed no abnormalities and there were no relationships between abnormal ventricular size and any clinical variables such as birth weight, language proficiency, developmental quotient and the like. A Swedish study showed an incidence of abnormal CT scans which was similar in groups of autistic and retarded children (i.e about one quarter).

Caparulo et al, have reported on a broad group of developmental neuropsychiatric cases of whom 22 were autistic. Two of the autistic children showed CT scan abnormalities involving increased ventricular size, one of these also showed EEG abnormalities. Two had 'mildly abnormal' scans. The actual percentage of autistic children in this study showing abnormal CT scans was markedly smaller than that of comparison groups of language disordered, attention deficit disordered, Gilles de la Tourette syndrome and retarded children. CT scans taken from nine high functioning classically autistic boys, by Prior et al [6] showed no abnormalities of any kind suggesting that perhaps it is only a subsample of autistic children with severe retardation and other organic signs who may have abnormal brain development identifiable by CT scan. None of the CT scan studies permits the conclusion that gross structural abnormalities are characteristic of autism.

Neurological models

A speculative neurological model for autism was elucidated by Damasio and Maurer [21]. Beginning from the observation that the abnormal behaviour in autism is comparable to that seen in brain damaged adults especially those with frontal lobe, basal ganglia, or limic system damage, they propose that 'autism is consequent to dysfunction in a complex of bilateral CNS structures that include mesial frontal lobes, mesial temporal lobes, basal ganglia.....and thalami.....' As evidence for this theory they cite the motility disturbances, abnormalities of muscular tone, posture, gait, and akinesia as signs of dysfunction of the basal ganglia, especially the neostriatum and of closely related structures of the mesial aspects of the frontal lobes. This also fits with the disturbances of communication, attention, and perception which can occur as a result of medial frontal lobe lesions and basal ganglia abnormalities and which are characteristic of autism. The ritualistic and compulsive behaviours commonly observed in autism are also seen in frontal lobe damaged patients especially with early sustained lesions. The inability to learn by experience, to adapt to changing environments, to organize appropriate responses are common to both autistic and frontal lobe patients. Preservation, lack of initiative, concreteness, shallow affect and lack of empathy similarity can be observed in autistic and frontal lobe damaged individuals. Hoffmann and Prior [35] have reported that autistic children show deficits in frontal lobe mediated behaviour, for example on the Milner maze test where their performance was characterized by inability to form plans or strategies, considerable preservation, inability to profit from feedback concerning errors, and lack of affective response to either correct or incorrect choices.

Whilst these hypotheses deserve further investigation, the leap from behavioural observation to physiological abnormality is a large one and in view of the lack of evidence for lesions in autistic

patients the proposed connections between frontal lobe damage and autistic behaviour remains a tenuous one.

A limbic system model proposed by Lamondella [36] suggests that the limbic system may be the site of dysfunction in autism. Since it is responsible for arousal, social interaction, emotion, sensory thresholds, attention to novel stimuli, as well as basic communication functions, Lamondella suggests 'intrinsically or extrinsically triggered limbic malfunctions is the cause of early infantile autism'. Limbic epilepsy may also be proposed as the cause of the increase in fits noted by so many authors in adolescent and adult autistic cases.

Though Lamondella's model is difficult to test and lacks support from any extant physiological or neurological studies it appears worthy of further exploration since it fits well with behavioural observations of autistic children, it incorporates the notions of critical periods and plasticity, it covers the most critical and basic aspects of autism, the social and communication deficits and it is not weakened by the findings so far of no particular structural deficits in the brains of autistic individuals. It also allows for some heterogeneity in symptomatology and could conceivably be elaborated to include some explanation of the fact that a proportion of autistic children do show normal intelligence, can develop language and can make a reasonable adjustment in later life.

Hoffman & Prior [35] have suggested that it appears that much of the behaviour of higher functioning autistic children at least, reflects mediation or control of function by the right hemisphere of the brain. We have shown that higher functioning autistic children perform according to their chronological age level on tests purporting to assess right brain functions but are grossly handicapped, in fact perform more poorly than mental age matched (and therefore younger) controls on tests purporting to asses left brain functions. There is in addition some evidence from dichotic listening studies suggesting abnormal lateralization of function [37]. It is not yet clear whether this pattern of performance in autistic children reflects immaturity (with right hemisphere and less mature strategies being used in all cognitively demanding situations) or whether there is in fact selective damage to the left hemisphere in a subgroup of autistic children who may have been able to compensate for such damage by greater right hemisphere development which permits the attainment of quasi normal intelligence except on tests of high language content.

There are a number of theoretical problems with this model especially since if autism has its onset early in life there ought to be more effective compensation for lateralized damage in the infant brain. Bilateral damage would have to be proposed for the low functioning majority of autistic children who share many of the behavioural symptoms while lacking the intellectual and language attainments of the high functioning group. If it were considered that the two groups represent different disorders of course this problem would be resolved in part at least. Reference to Kanners early discussions of the disorder suggest that early cases of infantile autism did not show the degree of global retardation which characterizes so many of the cases now called autistic. Despite these caveats there is some support for the proposals in a study of lower functioning autistic children using the Halstead Reltan Neurophysiological Test Battery for Children [38] where results essentially similar to those of Hoffman and Prior [35] were found with significantly greater left than right hemisphere of dysfunction. However Dawson was careful to note that only 5 autistic children showed left hemisphere impairment alone, with the remaining 5 with involvement of both hemispheres.

Lamondella [36] has suggested that the two hemispheres may process limbic input differentially. This allows some connecting threads to be drawn between his model and the hemispheric dysfunction

proposals. Lamondella notes support for the hypothesis of differential interaction of right and left hemisphere with limbic functions and suggests that integration of the two functional areas may occur via systems which could in turn be part of the limbic system. Further explorations of such an hypothesis may well be very profitable.

Conclusions

This review of biological factors in childhood autism has shown for the most part that we have made very little progress in the search for etiology. We must conclude that we are no closer to finding causes than we were thirty or forty years ago when the search began. There are some obvious reasons for this lack of progress which have been mentioned frequently in this paper. In summary they are:

(1) the use of heterogeneous samples of autistic children who whilst they all exhibit autistic behaviour do so for many different and sometimes obvious reasons;
(2) methodological and measurement problems in biological research which make findings difficult to replicate and to interpret;
(3) lack of normative developmental data in most of the areas studied making comparisons between autistic and other groups, of doubtful significance;
(4) failure to take account of retardation factors in sample selection and measurement;
(5) the primitive nature of our knowledge of brain physiology and the functional relationships between brain and behaviour.

It certainly appears at this stage that a search for a unique cause for autism based on the assumption that is a unique and specific childhood disorder may be fruitless. An important point for discussion then centres around the suggestion argued strongly by Wing and others and implied by many researchers who work with autistic children, that autism is not a specific disorder but can occur in many very different types of children with many different underlying problems.

1.Kanner L, Autistic disturbances of affective contact
Nervous Child Page: 2: 217-250, 1943
2.Lolter V, Epidemiology of autistic conditions in young children II. Some characteristics of the parents and children
Social Psychiatry Page: 1: 163-173, 1967
3.Prior M, Gajzago C & Knox D, An epidemiological study of autistic and psychotic children in the four eastern states of Australia
Australian & New Zealand Journal of Psychiatry Page: 10: 173-184, 1976
4.Rutter M, The development of infantile autism
Psychological Medicine Page: 4: 147-163, 1974
5.Hermlin B & O' Connor N, *Psychological Experiments with Autistic Children London: Pergamon*1970
6.Prior M, Tress B, Hoffman W & Boldt D, Computed tomographic study of children with classic autism
Archives of Neurology Page: 41: 482-484, 1984
7.Lalter V, Epidemiology of autistic conditions in young children
I Prevalence Social Psychiatry Page: 1: 124-137, 1966
8.Folstein S & Rutter M, Infantile autism: a genetic study of 21 twin pairs

Journal of Child Psychology & Psychiatry Page: 18: 297-321, 1977
9.Bartak L, Rutter M & Lox A, A comparative study of infantile autism and specific developmental receptive language disorder I The Children
British Journal of Psychiatry Page: 126: 127-145, 1975
10.Rutter M, The development of infantile autism
Psychological Medicine Page: 4: 147-163, 1974
11.August G, Steward M & Tsai L, The incidence of cognitive disabilities in the siblings of autistic children
British Journal of Psychiatry Page: 138: 416-422, 1981
12.Ritvo E, Spence A, Freeman B, Mason Brothers A, Mo A & Marazita M, Evidence for autosomal recessive inheritance in 46 families with multiple incidence of autism
American Journal of Psychiatry Page: 142: 187-192, 1985
13.DeMyer M K, Hingten J N & Jackson R K, Infantile autism reviewed: a decade of research
Schizophrenia Bulletin Page: 7: 388-451, 1981
14.Torrey E F, Nersch S P & McCabe K D, Early childhood psychosis and bleeding during pregnancy: A prospective study of gravid women and their offspring
Journal of Autism & Childhood Schizophrenia Page: 5: 287-297, 1975
15.Campbell et al, Demographic and perinatal profile of 105 autistic children: A preliminary report
Psychopharmacology Bulletin Page: 14: 36-39, 1978
16.Missing
17.Missing
18.Missing
19.Deykin E Y & MacMohan B, Incidence of seizures among children with autistic symptoms
American Journal of Psychiatry Page: 136: 1310-1312, 1979
20.DeMyer M K, Motor, perceptual motor and intellectual disabilities of autistic children. In L Wing (Ed)
*Early Childhood Autism. Second Edition, Oxford; Pergamon*1976
21.Damasio A R & Maurer R S, A neurological model for childhood autism
Archives of Neurology Page: 38: 777-786, 1978
22.Whitmont S, The power spectrum profile in autistic children
Australian Autism Review Page: 1: 27-33, 1982
23.Small J G, Cited in: DeMyer M K, Hingten N N & Jackson R K Infantile autism reviewed: a decade of research
Schizophrenia Bulletin Page: 7: 388-451, 1981
24.James A L & Barry R J, A review of psychophysiology in early onset psychosis
Schizophrenia Bulletin Page: 6: 506-525, 1980
25.Waldo M, Cohen D, Caparulo E, Young J, Parichard J & Shaywitz B, EEG profiles of neuropsychiatrically disturbed children
Journal of American Academy of Child Psychiatry Page: 17: 656-670, 1978
26.Ornitz E, Ritvo E, Brown M, LaFranchi S, Parmelee T & Walter R, The EEG and rapid eye movements during REM sleeep in autistic and normal children
Electroencephalography & Clinical Neurophysiology Page: 26: 167-175, 1969
27.Tanguay P, Edwards R, Buchwald J, Schwafel J & Allen V, Auditory brainstem evoked responses in autistic children
Archives of General Psychiatry Page: 39: 174-180, 1982
28.Porges S W, Peripheral and neurochemical parallels of psychopathology: A psychophysiological model relating autonomic imbalance to hyperactivity, psychopathy, and autism

Advances Child Development and Behaviour Page: 11: 35-65, 1976
29.Narasimhachari N & Himwhich H E, Biochemical studies of early infantile autism
Biological Psychiatry Page: 10: 425-432, 1975
30.Chess S, Autism in children with congential rubella
Journal of Autism & Childhood Schizophrenia Page: 1: 33-47, 1971
31.Chess S, Follow-up report on autism in congential rubella
Journal of Autism & Childhood Schizophrenia Page: 7: 68-81, 1977
32.Gillberg C & Forsell C, Childhood psychosis and neurofibromatosis - more than coincidence
Journal of Autism & Developmental Disorders Page: 14: 1-8, 1984
33.Meryash D L, Szymanski L & Gerald P S, Infantile autism associated with the fragile-X syndrome
Journal of Autism & Developmental Disorders Page: 12: 295-301, 1982
34.Campbell M, Rosenbloom S, Perry R, George A, Kricheff I, Anderson L, Small A & Jenings S, Computerized axial tomography in young autistic children
American Journal of Psychiatry Page: 139: 510-512, 1982
35.Hoffmann W & Prior M, Neuropsychological dimensions of autism in children: a test of the hemispheric of dysfunction hypothesis
Journal of Clinical Neuropsychology Page: 4: 27-42, 1982
36.Lamondella J, The limbic system in human communication In: H Whitaker & H A Whitaker (Eds) *Studies in Neurolinguistics, N Y Academic Press*1977
37.Prior M R & Bradshaw J L, Hemispheric functioning in autistic children
Cortex Page: 15: 73-81, 1975
38.Dawson G, Lateralized brain dysfunction in autism: Evidence from the Halstead-Reitan Neuropsychological Battery
Journal of Autism & Developmental Disorders Page: 13: 269-286, 1983