Chapter 15
Autism Spectrum Disorder: 70 Years on and the Plot Thickens

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1 Introduction

Autism spectrum disorder (ASD) is characterised by patterns of delay and deviance in the development of social, communicative and cognitive skills, arising in the first years of life.

In October 2010, Donovam and Zucker published an article in The Atlantic, "Autism's First Child" or "Leo Kanner's Case No. 1, Don T". The authors through painstaking detective work tracked down Donald who will be eighty this year.

In their own words, "*Later chapters in his life remained unwritten, leaving us with no detailed answer to the question: Whatever happened to Donald?*

There is an answer. Some of it we turned up in documents long overlooked in the archives of Johns Hopkins. But most of it we found by tracking down and spending time with Donald himself. His full name is Donald Gray Triplett. He's 77 *years old. And he's still in Forest, Mississippi. Playing golf*' (Donovan and Zucker 2010).

Oliver Triplett, the father, of Case No. 1, sent a preliminary report to Kanner that was 33 pages long. "Oliver's *observations were the first detailed listing of symptoms that are now instantly recognisable to anyone who knows autism.—The child was withdrawn* "*into his shell,*" *to* "*live within himself,*" "*perfectly oblivious to everything about him.*" "*No apparent affection*" "*a mania for spinning blocks and pans and other round objects.*" "*A fascination for numbers, musical notes, letters of the alphabet, which he enjoyed reciting in reverse order,*"*—he also had intense dislikes: milk, swings, tricycles*—"*almost a horror of them*" "*When interfered with, he has temper tantrums, during which he is destructive*".

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S. Malhotra and S. Chakrabarti (eds.), *Developments in Psychiatry in India*,
DOI 10.1007/978-81-322-1674-2_15

By the age of 2, he could recite the 23rd Psalm and knew 25 questions and answers from the Presbyterian catechism by heart.—And the random humming he engaged in while spinning blocks turned out not to be quite so random after all. Rather, he always "picked three notes that, if played simultaneously on a keyboard, would blend into a perfect chord" (Donovan and Zucker 2010).

To this Kanner, America's leading psychiatrist, at that time was to write these most famous words to Donald's mother, Mrs. Triplett:

> Nobody realizes more than I do myself that at no time have you or your husband been given a clear-cut and unequivocal … diagnostic term.";—"If there is any name to be applied to the condition of Don and those other children, I have found it best to speak of it as "autistic disturbance of affective contact" (Donovan and Zucker 2010).

These words were to mark the description of a new childhood condition, *infantile autism*, now called ASD. Kanner's original description still continues to form the core of the diagnosis of autism, a condition which is rapidly being reported across the globe and puzzling scientists, families and therapists. India too has published extensively in several aspects of the condition. This chapter will highlight Indian research while noting current world opinion.

2 Definition and Prevalence

2.1 Definition

Autism is now defined as a disorder characterised by the following:

(a) Deficits in social communication and social interaction manifested by all three of the following:

- Deficits in social–emotional reciprocity
- Deficits in nonverbal communicative behaviours used for social interaction
- Deficits in developing and maintaining appropriate relationships

(b) Restricted repetitive patterns of behaviour, interests or activities manifested by at least two of the following:

- Stereotyped or repetitive speech, movements or use of objects
- Excessive adherence to routines or rituals
- Restricted interests
- Hyper- or hypo-sensitivity to sensory stimuli

These symptoms should be noticed in early childhood and interfere with function. Three levels of severity are also included (American Psychiatric Association 2013).

2.2 Prevalence

The centre for disease control (CDC) has documented that more children are being diagnosed with an ASD than ever before. A conservative estimate is of 1/500 children. However, the CDC in 2008 reported the overall estimated prevalence of ASDs as 11.3 per 1,000 (one in 88) children aged 8 years. ASD prevalence

estimates varied widely across all sites (range: 4.8–21.2 per 1,000 children aged 8 years. The risk is 3–4 times higher in males than in females (CDC 2012).

In an important review commissioned by the WHO, in most studies reported after 2000, the median prevalence is 17/10,000 for AD and 62/10,000 for all pervasive developmental disorders (PDDs) (Elsabbagh et al. 2012).

Most reports from India tend to be from hospital-based samples. Erna Hoch, a Swiss psychiatrist, who worked in Kashmir, reported 2.9 % of cases in a missionary hospital to be infantile autism. Subsequently, patients were reported from tertiary care centres (Hoch 1967). One of the earliest studies was from Bangalore (Narayanan 1978).

The following studies from a tertiary care centre report clinic figures. Four patients were noted to have attended the outpatient clinic between 1981 and 1982 (Malhotra and Chaturvedi 1984). Another study found 16 children diagnosed with autism over a 2-year period (Singhi and Malhi 2001). Five patients with childhood disintegrative disorder were reported from 1980 to 1989 (Narayanan 1978) and three patients with Asperger's syndrome from 1989 to 1999. Between 1989 and 1999, 46 patients with autism spectrum disorder were seen, of which 22 had autism, 12 had childhood disintegrative disorder, 5 had atypical autism, 4 had Asperger's syndrome and 2 children had Rett's syndrome (Malhotra and Chaturvedi 1984; Singhi and Malhi 2001; Malhotra et al. 2003; Malhotra and Vikas 2005). Thirty-one patients were reported between 1981 and 1984 at a tertiary centre in South India (Bharat et al. 1997; Srinath et al. 1989). In another clinic in North India of 641 cases, 121 or 18.9 % had PDDs (Juneja et al. 2012).

Special schools have also yielded clusters of subjects with autism. Out of 500 special school children screened for autistic disorder, 74 were diagnosed with autism (14.8 %) (Subbalakshmi 2012). Through retrospective analysis of records of an early intervention programme (EIP), one study demonstrated that 4 % of children attending an EIP centre had autism (Kaur et al. 2006). In a study in Barwani district, in a total of 262 children with ID evaluated for psychiatric disorders, the following rates were observed: attention deficit hyperactivity disorder (ADHD), 6.5 %; autism and 4.2 % anxiety (Lakhan 2013). In the past, attempts have also been made to create a central registry of cases (Seth and Kalra 2006; Kalra et al. 2005). *However a cohesive picture of the prevalence and incidence of autism spectrum disorder is missing in India. It is imperative that epidemiological studies which are multi-centric, representative and well designed using an instrument with high fidelity be carried out* (Sharan 2006).

3 Aetiology

The quest for the aetiology of autism has generated an astounding amount of research. Different theories abound with genetic, immunological, epigenetic, and environmental effects.

There is a good body of research from India, particularly in the study of genes that have been implicated as relevant.

(i) **Genetic factors**

In a review in the Pediatric Clinics of North America, the genetic and chromosomal disorders associated with autism were categorised as metabolic, mitochondrial,

chromosomal and single-gene conditions (Torielo 2012). The metabolic disorders were phenylketonuria, purine metabolism disorders, succinyl semialdehyde dehydrogenase deficiency, disorders of creatine transport metabolism, cerebral folate deficiency and Smith–Lemli–Opitz syndrome. Mitochondrial involvement was suggested by elevated lactate levels and respiratory chain disorders. The chromosomal anomalies were Dup7q11.23, Dup or Del 16p11.2, Del 17q12, Del or dup 15q13, and Del 22q13.

Under the monogenic conditions were listed Rett's, Angelman's, CHARGE and Cornelia de Lange syndromes, neurofibromatosis, tuberous sclerosis, myotonic dystrophy and Fragile X syndrome (Torielo 2012). Whereas in the past, the focus was on a search for a chromosomal cause, chromosomal microarray analysis (CMA) has identified copy number variants in as many as 8 % of children (Tchaconas and Adesman 2013). The interplay of several genes is now considered as aetiologically important. Genome-wide association studies suggest that a propensity to ASD appears to stem from common genetic polymorphisms, which exert substantial additive genetic effects on ASD (Klei et al. 2012).

5HIAA and HVA: Studies from India reflect the quest for aberrant gene transmission in families. In an early Indian study, 5HIAA and HVA was not increased in the CSF of 17 children with autism (Narayan et al. 1993).

Glutamate: In a study of 10 children with ASD and 10 controls, blood glutamate levels were measured using high-performance liquid chromatography technique, and brain glutamate levels were measured using proton magnetic resonance spectroscopy (MRS). The levels of glutamate were significantly raised and correlated with each other (Choudhury et al. 2012).

Tryptophan hydroxylase 2: Based on the premise of serotoninergic pathway involvement as an endophenotype for ASD, the association of tryptophan hydroxylase 2 (*TPH2*), the rate-limiting enzyme in 5-HT biosynthesis, and integrin beta-chain 3(*ITGB3*) a serotonin quantitative trait locus with ASD was investigated in the Indian population. The results indicated the likely involvement of *ITGB3* and *TPH2* in the pathophysiology of ASD in the Indian population (Singh et al. 2013).

Folate pathway: Folate pathways were assessed in 138 children with autism and 138 children without autism and were tested for 5 genetic polymorphisms related to the folate pathway. Of the genes studied using PCR-restriction fragment length polymorphism were methylene tetrahydroflate reductase (MTHFR C677T and MTHFR A1298C). MTHFR C677T was found to be a risk factor with MTHFR A1298C acting additively to increase risk (Mohammad et al. 2009).

Serotonin transporter gene (*SLC6A4*): Hyperserotoninemia, response to SSRIs and linkage to 17q11, has generated interest in studying the serotonin transporter gene SL6A4 (solute carrier family 6). The serotonin transporter gene (SLC6A4) was studied in 93 children with autism, their families and 160 controls. No preferential allelic transfer to the probands was noted (Guhathakurta et al. 2008).

Engrailed 2 (*EN2*): The epigenetic evaluation of *EN-2* a homeobox transcription factor, in the cerebellum of patients with autism indicates a persistent upregulation of a gene that normally undergoes perinatal downregulation to ensure normal Purkinje cell differentiation. *EN-2* has now been verified to be one of several candidate genes that have both genetic and epigenetic associations with autism including brain-derived neurotrophic factor, the reelin gene (RELN),

oxytocin, HOXA1, MeCP2 and screening for Fragile X (FXS; Tr Psyr). A study in Assam of Engrailed 2 (EN2) involved in the patterning of the cerebellum in development has been found to map to the 7q36.3 region, which has previously been shown to be associated with ASD and language disorders like childhood dysphasia. Five markers in the promoter, exon 1 and intron region of the EN2 gene were studied. Two intronic markers were transmitted with a significant bias in favour of females, which has not been reported before (James et al. 2013; Sen et al. 2010).

Reelin gene: The RELN is located on chromosome 7q22, an important and critical region for autism, identified through several genome-wide scans. The first of the two studies from Assam was conducted with 73 persons with autism and 129 parents and 80 controls. There was no difference in allelic and genotypic distribution between patients and controls. Though there was a difference in allele repeats between Indian and other populations, there was no difference between patients and controls in the three markers of the RELN (Dutta et al. 2007). A subsequent study investigated six more single nucleotide polymorphisms (SNPs) in 102 patients, 182 parents and 101 healthy controls. No preferential parental transmission of any alleles of the markers to affected offspring, or any biased allelic or genotypic distribution between the cases and controls was noted (Dutta et al. 2008). Thus, this study suggested that SNPs of RELN are unlikely to be associated with ASD in the Indian population.

Glutamate 6 receptor: Glutamate receptor 6 gene (GLu R6 or GRIK2) was studied in 101 cases, 180 parents and 152 controls, but no biased transmission of alleles or haplotypes to the affected offspring was detected (Dutta et al. 2007).

Glutathione S-transferases: Glutathione S-transferases (GST) are antioxidant enzymes that play an important role in the cellular detoxification and have been associated with ASD. Six patients with ASD and 8 controls were assessed for GST activity. Fifty one patients with ASD and 45 controls were recruited for GST mu (GSTM1) and G theta (GSTT1) genotyping. While no significant differences in frequencies of GSTM1 and GSTT1 genotypes was noted, the mean erythrocyte GST activity in ASD was significantly decreased compared with controls (Hermawati et al. 2011).

*HOXA1 and HOXB*1: Some negative correlations and lack of association of HOXA1 and HOXB1 variants with autism in an Indian study (Gangopadhyay et al. 2007).

Fragile X screening and checklist: The Fragile X syndrome is the most frequent hereditary cause of mental retardation. It has been the focus of several studies. The *FMR1* gene is classified into normal 5–44; gray zone 45–54; premutation 55 to <200; and full mutation ≥200 repeats. About 705 women from Tamil Nadu, South India, were screened for the *FMR1* allelic variation by using radioactive polymerase chain reaction–polyacrylamide gel electrophoresis (PAGE) analysis. One in 353 women carried the premutation. No full mutations were observed. Ms-PCR is more suitable for routine screening and clinical testing compared with rPCR-PAGE analysis. In a study reporting screening for Fragile X (FXS) in 157 individuals with various neurobehavioural problems, only four were confirmed as FXS (3.18 % prevalence among neurobehavioural outpatients). Thirty distinct alleles with 12–49 CGG repeats were detected, by the FRAXA checklist. In a clinically useful study, when clinical features were analysed in 327 males and 41 females, six clinical features were statistically significant in FRAXA individuals, namely hyperactivity, poor eye contact, hyperextensibility of joints, large ears,

macro-orchidism and a family history of mental retardation. Using this checklist would improve the reliability of FRAXA testing (Manjunatha et al. 1989; Rai 2011; Indhumathi et al. 2012; Bhowmik et al. 2009; Guruju et al. 2009).

Fragile sites: In 150 subjects selected from 140 families, 132 families had a single child with autism, while in 8 families, multiple sibs were affected. Among the 150 subjects analysed for various fragile sites, 12 individuals were found to be positive for Fragile "X" chromosome (Manjunatha et al. 2001).

Tuberous sclerosis complex: Tuberous sclerosis complex (TSC) is an autosomal dominant disorder with loci on chromosome 9q34.3 (TSC1) and chromosome 16p13.3 (TSC2). In a study, a total of 12 mutations were studied; of these, seven mutations were novel. A single previously known deletion in the TSC1 gene was identified. In addition, three and eight variants/polymorphisms in the TSC1 and TSC2 genes, respectively, were detected. Of these, three were novel SNPs (Ali et al. 2004).

MRNA: A systematic analysis of the CNV-miRNAs based on their interactions with the target genes enabled the identification of top 10 miRNAs as hub molecules. These CNV-miRNAs in turn affected transcription factors and their target genes with a role in neurodevelopment and synapse formation. This was possibly the first report to highlight the significance of CNV-microRNAs and their contribution towards the genetic heterogeneity of autism (Vaishnavi et al. 2013).

Systems biology: Using a systems biology approach, starting with 675 genes for ASD and 713 genes for bipolar disorder and using a consensus path database, networks for 4 pathways were identified: (1) neuroligand receptor interaction pathway, (2) synaptic transmission, (3) circadian rhythm pathway and (4) catecholamine synthesis pathway (Ragunath et al. 2011).

Twin studies and the shared environment: It needed a twin study done in California to highlight the importance of a shared environment in contributing to concordance. Structured diagnostic assessments were completed on 192 twin pairs. For strict autism, concordance for male twins was 0.58 for 40 monozygotic pairs and 0.21 for 31 dizygotic pairs; for female twins, the concordance was 0.60 for 7 monozygotic pairs and 0.27 for 10 dizygotic pairs. The conclusion was that the susceptibility to ASD has moderate heritability and a substantial shared twin environmental component (Surén et al. 2013).

(ii) **Immunological factors**

Immune function alterations have been repeatedly demonstrated in patients with autism and their families. These include neuroinflammation in brain tissue, elevated cytokines in blood and CSF and antibodies directed against neural tissue (Vargas et al. 2005). Infections may also contribute to immune dysfunction. Cytokines implicated in autism are IL-1B, IL-6, IL-4, IFN-γ and TGF-B (Tchaconas and Adesman 2013; Vargas et al. 2005; Onore et al. 2012; Singh 1996).

Nuclear factor kappa B (*NF-κB*): A clear period of normal development followed by regression and subsequent improvement with treatment suggests a multifactorial aetiology. Viral and bacterial infections, hypoxia or medication could affect both the foetus and the infant. These stressors could upregulate transcription factors like nuclear factor kappa B (NF-κB), a master switch for many genes including some implicated in autism like tumour necrosis factor (TNF). Based

on this hypothesis, one Indian study chose to determine NF-κB in children with autism. Peripheral blood samples of 67 children with autism and 29 control children were evaluated for NF-κB using electrophoretic mobility shift assay (EMSA). A significant increase in NF-κB DNA binding activity was noted in peripheral blood samples of children with autism. As NF-κB levels reflect a response to stressors of several kinds, and in turn NF-κB controls many genes, the significance of its role in autism needs further elucidation (Naik et al. 2011).

Allergies: *Ninety-four* serum samples of patients were tested for IgG. Although egg, milk, wheat, peanuts and buckwheat are the most common food allergens, in this study, egg allergy was seen in 5.08 % of patients, milk allergy was seen in 7.62 % and wheat flour allergy was seen in 5.93 % of patients. Peanut allergy was seen in 47.45 % of the subjects (Rao 2010).

(iii) **Environmental factors**

Environmental toxins include heavy metals like lead and mercury; pesticides like organochlorines, organophosphates, and pyrethoids; and two halogenated aromatic hydrocarbons, namely polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs). Recently, PBDEs have been shown to influence the expression of autism-related genes in the brain of experimental animals and human brain tissue. The role of environmental factors in earlier described mechanisms like cytokine regulation reflects a close interplay of the environment with immune mechanisms (LaSalle et al. 2013; Goines and Ashwood 2013).

Folate intake: In a Norwegian cohort that enrolled 109,000 children born from 2002 to 2008, the mothers were recruited during pregnancy at approximately 18 weeks' gestation. It was found that those mothers who started taking folic acid before getting pregnant were about 40 % less likely to have a child who developed autism. Folic acid supplements were best started 4 weeks before conception. In children whose mothers took folic acid, 0.10 % had autistic disorder, compared with 0.21 % in those unexposed to folic acid. This finding has a simple lesson of supplementation of folic acid before conception as preventive strategy (Hallmayer et al. 2011). Also implicated have been maternal infections in pregnancy, low birthweight, increased paternal age and twin pregnancies (Tchaconas and Adesman 2013).

Trophoblastic inclusions in the placenta: An interesting new study suggests that examining the placenta for trophoblastic inclusions may help predict autism in high-risk infants (Walker et al. 2013).

Toxins (*trace elements percentage and toxic elements*): In 45 children with autism and 5 controls, levels of copper, polybenium and mercury were significantly higher in the hair and nails of children with autism, with direct relation to severity. The trace elements magnesium and selenium were reduced in children with low-functioning autism (Priya and Geetha 2011).

Oxidative stress markers: Urinary levels of oxidative stress markers, namely thiobarbituric acid-reacting substances, lipid hydroperoxides, 4-hydroxynonenal, protein carbonyls, sulfhydryl groups, total antioxidant capacity, total peroxide content, oxidative stress index and also UA/Cr ratio, can be considered as the measure of oxidative stress index in children with autism. The significant correlation between severity of autism and urinary lipid peroxidation products also supports

the use of oxidative stress markers and antioxidants as biomarkers of autism (Damodaran and Arumugam 2011). A recent brief report discussed the possibility of vitamin B12 deficiency as a causative mechanism in a patient with childhood disintegrative disorder (Malhotra et al. 2013).

Mouse models: Valproic acid was used as a toxicant in mice with a deletion of glutathione-S-transferase M1 (GSTM1), a gene associated with increased risk of autism that codes for an enzyme involved in the management of toxicant-induced oxidative stress. Valproic acid treatment caused significant increases in apoptosis in granule cells of the hippocampus and cerebellum. Valproic acid treatment resulted in deficits in social behaviours, not found in control mice without the gene deletion (Yochum et al. 2010).

Electromagnetic fields: Electromagnetic fields emitted during the operation of electronic gadgets do not have enough energy to cause DNA alterations directly; however, ample evidence is available from in vitro and in vivo studies to demonstrate their ability to cause DNA alterations indirectly as well as epigenetic modifications (Ahuja et al. 2013).

(iv) **Neuroimaging**

The three methods used for imaging in autism are positron emission tomography (PET), single-photon emission tomography (SPECT) and MRS. Three neurotransmitters have been studied: serotonin, dopamine and amino butyric acid (GABA). PET studies have shown a prolonged period of higher brain levels of serotonin synthesis, and also asymmetries of marker uptake in the thalamus, cerebellum and frontal cortex. SPECT studies have shown increased whole brain dopamine binding. MRS studies have shown decrease in *N-acetyl aspartate* (NAA) levels in children with autism (Chugani 2012). In a SPECT study of 22 children with autism, fifteen children had no perfusion abnormalities on SPECT imaging. Of the remaining seven, decreased perfusion in the left frontoparietal cortex was seen in three children and in the left inferior and medial frontal cortex in two children (Singhi et al. 2008). In another SPECT study, 10 children, with ASD, showed hypoperfusion in frontal prefrontal and subcortical areas (Gupta and Ratnam 2009). In a third study, temporal tubers were found to correlate with symptoms of autism in children with TSC (Kothur et al. 2008).

(v) **Psychological theories and birth-related issues**

Psychological stressors: Pathological changes in the cerebellum in autism are thought to correspond to an event before 30–32 weeks' gestation. Incidence of stressors during each 4-week block of pregnancy was recorded. Incidence of stressors in the blocks prior to and including the predicted time period (21–32 weeks' gestation) in each group of surveys was compared to the other prenatal blocks. A higher incidence of prenatal stressors was found in autism at 21–32 weeks' gestation, with a peak at 25–28 weeks. This does support the possibility of prenatal stressors as a potential contributor to autism (Beversdorf et al. 2005). In an early Indian case series, four cases were reported where children manifested symptoms of autism after severe psychological stress (Kapur 1989).

Cultural issues: Many cultural issues can change the identification, help-seeking behaviour and diagnosis of children with ASD. African Americans were 2.6 times

less likely to receive a diagnosis of autism on their first specialty visit but instead were labelled ADHD (Mandell et al. 2007). Some traits of Asian children like avoiding eye contact with elders may be a sign of respect and not ASD. Studying Indians outside India, in a survey of 24 families with children with autism, three groups of families emerged: (i) primarily Western in their beliefs, (ii) primarily Indian and (iii) endorsed a combination of Western and Indian beliefs and practices. The observation was that when working with culturally diverse families, it is best not to assume the group as homogenous (Ravindran and Myers 2012).

Traits: In an interesting cross-cultural study, the expression of autistic traits were compared in students from three cultures the UK, India and Malaysia, using the autism spectrum quotient (AQ). Behaviours associated with autistic traits were greater in the Eastern group. Males scored higher than females, as did science students versus non-science students; Indian students scored higher on the imagination subscale and Malaysian students on the attention switching subscale (Freeth et al. 2013).

(vi) **The gut microbiome**

Newer research avenues have been explored in the past few years. The gut microbiome estimated "that up to a hundred trillion microbial cells have made a home of us". The human microbiome project was started in 2007 at the National Institute of Health (NIH), USA, to establish the nature of these organisms and their genome. The impact of this unrecognised "organ" in neurological and psychiatric disorders, and more particularly autism is under scientific scrutiny (Mulle et al. 2013).

It is obvious that there is no single aetiology for ASD. A complex array of genetic, environmental, epigenetic and psychosocial stressors may function in an untold number of permutations and combinations to lead to a clinical diagnosis.

4 Symptoms and Nomenclature

On 18 May 2013, Jeffery A. Lieberman, Director of the National Institute of Mental Health (NIMH), USA, issued a joint statement, with the President of the American Psychiatric Association (APA).

> This week, my good friend and colleague Tom Insel and I issued a rare joint statement clarifying the National Institute of Mental Health's (NIMH) support of the Diagnostic and Statistical Manual of Mental Disorders (DSM) as the gold standard of care for 2013 and for years to come. We did this because of a blog post on the NIMH Website about our collective frustration with the progress of brain science, the paucity of new treatments for brain diseases to help our patients and the need for future-looking researchers to think outside the box. We were concerned that comments about how to move beyond some of our traditional, symptom-based methods of diagnosis—which are, at the moment, the gold standard of science—were widely misreported as NIMH changing its position on the newly revised DSM-5. This is, of course, a preposterous notion. The NIMH was involved in all phases of the revision of the DSM, including the moments during the 10-year process when we all realized that the science that we hoped by now would have given us laboratory, imaging and electrophysiologic procedures to help diagnose mental illnesses was still coming up short (Jeffrey and Lieberman 2013).

The disappointments of the past 20 years are that we are still a phenomenological group struggling to find our disease markers. Of course, one must not forget that

finding clear biochemical or imaging tests will promptly take the condition away to other disciplines! One important study conducted by Daley in India was assuring, as the majority of psychiatrists, paediatricians and psychologists used the ICD-10 or the DSM-IV for diagnosis (Daley and Sigman 2002). In 2010, data from 643 paediatricians in 1998 and 643 paediatricians in 2008 suggested a greater awareness and recognition of cases was reported with appropriate criteria for diagnosis (Daley and Barua 2010). It would be interesting to see the response to the new DSM criteria, while experts in the USA like Volkmar and Reichow (2013) have diametrically opposite views on the changes in the autism category. The main concern is that with greater specificity, some sensitivity will be lost and milder forms of the disorder and high-functioning individuals will not receive a diagnosis and therefore no treatment.

The symptomatology of autism began with Kanner's case notes. While gathering material for this paper, one reference turned up "India" in a Kanner article, called "*The conception of wholes and parts in early infantile autism*". What was the reference to India?

In one of the early cases, Malcolm H. saw a picture in an encyclopaedia. His mother said it was the *Taj Mahal in India—He then went through the whole library for days searching for pictures of India (Taj Mahal)*—"He was disturbed because the next two pictures of the Taj Mahal were different and "*found solace in getting the encyclopaedia and looking at the picture he had seen there first*" (Kanner 1951).

Leo Kanner's amazing attention to detail cannot be matched, and symptom descriptions like these still form the basis of a diagnosis of autism.

In India, Tito, an exceptionally bright but less verbal adolescent, wrote an insider's view of autism through three books written when he was 8, 11 and 17 years of age. Writing in the third person about "the boy," he writes:

> The hand had made a strange relationship with its shadow and he fluttered it and spent his hours contented with the lone company of his shadow. And his worries stopped. He shut away the world and felt secure in the presence of the shadow. If only the world could be a game with the shadow. But the reality was that he was drawing himself away and away into the world of his shadow. Nights were terrible. He searched everywhere for his shadow. He flapped to call it, there was nothing but darkness. He cried for it betrayed by the friend (Tito).

When asked why he flapped, he replied in writing, "*I am calming myself. My senses are so disconnected, I lose my body. So I flap. If I don't do this, I feel scattered and anxious*" (Mukhopadhyay 2000). Sceptical BBC producers documented his story with amazement, and his mother Soma has gone on to describe her treatment strategies based on her care of Tito and his feedback.

Several updates to symptomatology are added regularly to the world literature (Nazeer and Ghaziuddin 2012). The literature on symptomatology in the Indian literature mainly comprises case reports. There is also a wealth of unpublished literature. Clinical observations date back to 1978 (Narayanan 1978). Some of the case reports are on childhood disintegrative disorder, Rett's disorder, CHARGE syndrome and tuberous sclerosis (Malhotra and Singh 1993; Malhotra et al. 2002; Malhotra and Gupta 2002; Kumar et al. 2004; Sitholey et al. 1998). A descriptive hospital-based study was published in 2005 (Pushker et al. 2012). Disorders in speech articulatory function have been reported, which might serve as early indicators (Juneja et al. 2005). In vernacular speech, in Malayalam-speaking children,

echolalic ability was observed to be present independent of the general language ability (Sullivan et al. 2013). Fifteen children with ASD were compared with 10 controls for speech abnormalities: exaggerated pitch, pitch range, pitch excursion and pitch contours were observed in autism. These are distinctive characteristics of *motherese,* suggesting a distinct vocal output (Aithal et al. 2011).

Pull to sit and hypotonia: A head lag at 6 months appeared to predict autism and could be evaluated further as an early marker (Sharda et al. 2010).

Log reports of time spent: In one interesting study of 140 preschool children with developmental disability, hourly log reports of time spent demonstrated differences between children with ASD from the rest of the group. Children with ASD spent thrice the time on sedentary or exclusion activities like watching television (21 % of the time) or playing alone (14 %). Conversely, playing with peers was 1.7 % and home schooling 0.3 % of the time (Shah 2012).

Epilepsy and neurological symptoms: The figure for epilepsy in autism varies at approximately 30 % before adolescence—with two peaks, one in early childhood and again in adolescence (Venkatesan 2005). Abnormalities in auditory brain stem responses were described (Silver and Rapin 2012). In a study to compare the developmental profiles of children with autism and children with developmental delay, the children with autism showed lower social skills, whereas children with developmental delays showed poorer motor skills (Shivashankar and Satishchandra 1989).

Intelligence: Data on intellectual ability from seven sites were combined; 38 % of children with ASDs were classified in the range of intellectual disability (ID) (i.e. IQ $\leq$ 70, 24 % in the borderline range (IQ 71–85) and 38 % had IQ scores >85). The proportion of children classified in the range of ID ranged from 13 % in Utah to 54 % in South Carolina (CDC) (CDC 2012). Michael Rutter, the doyen of child psychiatry and authority on autism, discussed the following areas to be evaluated in ASD, namely developmental regression, savant skills and epilepsy and additional psychiatric diagnosis. To these may be added sleep disorders, which are so characteristic of ASD (Jayarama and Bhat 2004).

Regression: Regression is defined as the loss of previously acquired skills. About Kanner's Case No. 3, his parents stated "*It seems that he has gone backward mentally gradually for the last 2 years*". At the current time, as Ozonoff stated in 2010, "Behavioural signs of autism are not present at birth but emerged through diminished social communication behaviours. More children may present with regression than previously thought, but parent reports do not capture this phenomenon". While gaze, smiles and vocalisations were mostly comparable at 6 months, infants who later went on to receive a diagnosis of ASD showed distinct differences by 12 months of age (Rutter 2011). Regression is determined through retrospective parental accounts, prospective laboratory studies and home video recordings which complement parent reports, counts or when a child cannot come into the laboratory to be observed (Ozonoff et al. 2010). According to Ozonoff, 19 of 22 young children who went on to develop autism showed a decline in gaze directed to faces between 6 and 36 months of age. However, only three parents reported any regression in their child's behaviour (Rutter 2011). In our own experience, parents have initially not reported any regression, and later acknowledged regression while participating in parent groups. When asked why, one mother said she did not wanted to be labelled as a mother

who had missed the early signs of autism, in her son. In one study, 35 children with ASD and regression were compared with 35 children with ASD without regression. The mean age of regression was 22 months with the majority regressing between 12 and 24 months (Jones 2012). A single patient with regression also responded well to a comprehensive multimodal treatment approach in motor, language and social domains, and also in the activities and skills of daily living (Malhi and Singhi 2005). In a study of 51 children, regression occurred in 68.4 % of the sample; 21.5 % regressed before 12 months, 41.1 % regressed between 12 and 24 months, and 5.8 % regressed between 24 and 36 months (Nizamie et al. 2010). When the milestones of very young children with regressive autism are studied, it becomes likely that regression may have occurred even before the regression with clear-cut behaviour change, for which help is being sought. A child may have normal development for social smile and eye contact, but be delayed in stranger anxiety with the simultaneous onset of sensory issues. The difference between infants who regress and infants who do not may be in terms of change in those who regress and delay in those who do not (Abbagani 2006). This could well lead to the parent reporting that the child had multiple regressions at 15–18 months. Descriptive terms like "shy, stubborn and scared" were more often used in the non-regressive behaviour. In another small study of 31 children with regression and 37 normally developing children, regression was assessed on the following: turning to sound or name, carrying out commands, pointing waving bye-bye, speech, eye contact, self-help skills, indication of toilet needs, quality of play, interests, curiosity and sleep routines. These questions had good discriminatory value as only one normally developing child had regression (in toilet skills for a brief period after joining school). It was found useful in data retrieval to ask parents about each milestone, not only the time of achievement of the milestone but also if the achieved language or social skills had changed in any qualitative way. Our study found the following: turning to sound or voice, eye contact, socialisation, speech or vocalisation and sleep as the most frequently noted indicators of regression. Of these, 1–3 have been used to document regression based on home videos (looks at people, smiles at people, language and joint attention). The consensus is on prospective data collection and development of simple screens to sensitise paediatricians to the earliest behavioural manifestations of autism. This would lead to early identification, referral, evaluation and treatment without necessarily labelling a child (Abbagani et al. 2008). In a recent workshop, the participants also agreed to consider regression in autism as distinct from CDD, which is characterised by a very severe and rapid loss of skills after 2 years of age (Ozonoff et al. 2010).

Sleep disturbances: Children with ASD more prone to sleep disturbance and in an earlier study 40–80 % reported problems of sleep. Problems described have been in all areas of sleep: problems in onset of sleep, sleep maintenance, settling and nocturnal awakening. In children with ASD, nocturnal awakening may be characterised by laughing, vocalisation, screaming and playing alone with toys and objects (Naik et al. 2012). In one study, 51 children between the ages of one-and-a-half and six years with ASD and abnormalities in the development of sleep–wake cycles were seen in 62 % of children with autism. Resistance to sleep and waking were the most frequently reported. Sleep patterns included difficulty falling asleep, having disturbed sleep and waking

up at night (Nizamie et al. 2010). In another study, using the Owen's "The Children's Sleep Habits Questionnaire" (CSHQ), 27 children with regressive autism were compared with 37 typically developing children. Significant differences were found in regularity of bedtime, sleep duration, bedtime resistance, latency and night wakening. In addition to the quantitative aspects of sleep disturbance, noteworthy were the following qualitative aspects: complex bedtime routines which included rocking, swinging, and clinging to objects; excessive need for silence and darkness, and long car rides; special objects needed to sleep, e.g. a blanket to chew on, plastic bottles, lids, and toothpaste tubes; night awakening quality like, crying, screaming, playing with non-toys disregarding parent, watching television, and difficulty in returning to sleep; and unusual activities like walking over sleeping parents or siblings. These sleep-related issues contributed greatly to parental stress and coping abilities (Cortesi et al. 2010). The cultural aspects of sleep arrangements, like *Child falling asleep in Parents' bed* (To the Indian Parent this is normal), or *Item 3 Child falls asleep in own bed* (Often, no separate bed is available for a small child even in affluent families), need to be considered. These cultural differences can have international consequences. An Indian family in Norway could not explain their differences in child rearing practices and sleeping arrangements, to child health authorities with serious turmoil all round (Abbagani et al. 2012).

Savant skills: ASD has been associated with special skills often highlighted in films like "Rain Man" and books like "The curious case of the dog in the night time" (The Hindu 2012). In a very well-designed study, savant skills were specified as "an outstanding skill/knowledge clearly above participant's general level of ability *and* above the population norm." Exceptional cognitive skills were defined as applied to Wechsler subtest scores at least 1 standard deviation above general population norms, and 2 standard deviations above the participant's own mean subtest score. Twenty-four out of 93 individuals were identified as having one or more savant skills (total = 26 %). There were 14 calendrical calculators, four others with computational skills and three individuals with superior visuospatial skills. One individual had a musical talent, one had an exceptional memory skill, and one had skills in both memory and art (Greenwell 2004). Understanding strengths may help optimise a child's outcome, if these strengths are properly recognised and channelized (Howlin et al. 2009). In a review of 51 patients, parental report suggested 39 out of 51 children had exceptional skills in some area of cognition, amounting to 75 % of children, but no testing was done to verify the true nature of these abilities (Nizamie et al. 2010).

Differential diagnosis and comorbidity: Comorbidity of other conditions in autism has been well documented. The first step is ascertaining the presence or absence of ID, in which global developmental delay will be present, unlike in autism where abilities and deficits are not uniform. If there is no ID, ADHD, anxiety, mood disorders and psychosis should also be considered high incidences of coexisting ID have been reported in different studies, as high as 95 % (Seth and Kalra 2006; Nazeer and Ghaziuddin 2012; Gupta and Maitra 2002; Kar et al. 1993). The prevalence of comorbidities was found to be high, and it increased with severity of ID, except for ADHD, autism and violent behaviour, which decreased (Purkayastha et al. 1997). In children with ID in the Barwani district, ADHD was diagnosed in 6.5 % of children and autism in 4.2 % (Lakhan 2013).

Differential diagnosis: Differential diagnosis has not been discussed much in the literature. A study discusses the need to keep in mind language and learning disorders (Jauhari et al. 2012).

Bipolar disorder is hard to recognize in children with autism. ADHD, anxiety, depression and OCD are other comorbid conditions (Jayarama and Bhat 2004). In reporting diagnostic overshadowing, the example of study of a 9-year-old female child was cited. In a 5-year follow-up of a patient with an initial diagnosis of separation anxiety disorder during the course of follow-up, the child began to exhibit features of PDD, not otherwise specified (Baird et al. 2001).

The core symptoms still define ASD. However, regression and savant skills make the condition unique and mysterious.

5 Assessment

Reaching care has different routes. Who makes the diagnosis? Fortunately, the medical fraternity in the country appears to be following the ICD 10 or DSM IV with reasonable uniformity over the pattern of diagnosis. Level 1 screening measures are intended to be used by physicians to differentiate children at risk for ASDs from healthy children. Level 2 tools are used in developmental clinics to differentiate those at risk for having ASDs and other developmental disabilities, and as part of a diagnostic evaluation (Meera et al. 2012). These include the Autism Behaviour Checklist (ABC), the Childhood Autism Rating Scale (CARS), Gilliam Autism Rating Scale (GARS-2), the AQ, adolescent version, and the Social Communication Questionnaire (SCQ).

Brief Infant–Toddler Social and Emotional Assessment: The Brief Infant–Toddler Social and Emotional Assessment (BITSEA) subscales were evaluated in detecting risk for 456 toddlers. Results provided support for the BITSEA as a Level I screener for social emotional problems and a Level II screener for ASD symptoms at community sites such as well child clinics (Dyches 2011).

Assessment Kit for Autism (*AKA*): The action for autism (AFA) has made a new tool kit, and this needs to be used in a standardised manner through training to unify assessment and is intended to ensure that more and more children can be identified early. The AKA has three components:

1. A “quick scan” of child behaviours, completed by asking parent or persons who spend most time with the child a set of five questions.
2. Suggested activities for the professional to conduct, which will provide more information on the child’s behaviours.
3. Suggested questions for people who spend the most time with the child to get information about usual patterns of behaviour and activity, since all the relevant information may not be evident in one sitting with the child (Gardner et al. 2013).

Indian Scale for Assessment of Autism (*ISAA*): The NIMH Hyderabad has developed the ISAA based on the CARS. It has 40 items and six domains: social relationship and reciprocity; emotional responsiveness; speech language and communication; behaviour patterns; sensory aspects; and cognitive component. It has been used with success in clinic settings (Singhal: http://www.autism-india.org).

The Vineland Adaptive Behaviour Scales: The Vineland Adaptive Behaviour Scales-II edition, 2005 (Vineland-II), is useful in assessing abilities in autism spectrum disorder. Difficulties in administration of the scale to Indian children are related to cultural differences in gender roles and in the way some self-care tasks are performed (Patra and Arun 2011).

The CARS: The CARS has been evaluated for use in the Indian population, and with a CARS score of 33, a sensitivity of 81.4 % and a specificity of 78.6 % for diagnosis of autism have been found. There was high concordance with ICD-10. Another expert recommended the scale for use in the Indian context. In a study of 51 children with autism (DSM IV), the mean CARS rating was 44, while when the suggested cut-off of 67 was used, only 40 of 51 children were diagnosed to be autistic. It was suggested by the authors that the cut-off should be lowered to 45 to increase sensitivity in the Indian context (Manohari et al. 2013).

The Aberrant Behaviour Checklist has been validated internationally between a special school in Vishakhapatnam and a Swiss Institute (Russell 2010).

The Autism Behaviour Check list has also been studied in the Indian context (Varisco et al. 2009).

The Parenting Stress Index: The Parenting Stress Index (PSI) is a scale specifically developed to assess the magnitude of parental stress in various disorders. In a study, it was used to quantify stress experienced by 51 mothers of children with autism, before and after psychosocial and other interventions, with a follow-up period of 18 months. Significant improvement was seen in the parental subdomains of competence, attachment, role restriction, depression, isolation and health ratings following intervention, suggesting the usefulness of this tool in measuring change in parental stress (Juneja et al. 2010).

Too many tools: A recent study examined the measurement tools and target symptoms/skills used to assess treatment response during ASD intervention trials from 2001 to 2010. Data from 195 prospective trials were analysed. There were 289 unique measurement tools, of which 61.6 % were used only once, and 20.8 % were investigator designed. Only three tools were used in more than 2 % of the studies, and none were used in more than 7 % of studies (Abbagani et al. 2013). There is an obvious lack of consensus in the area of outcome measurement, which needs to be addressed. These results represent a lack of consistency in outcome measurements in ASD intervention trials. These findings highlight the need to set guidelines for appropriate outcome and assessment measures.

In general, assessment is one area where appropriate tools have been developed, which may need cross-validation in some cases, but some kind of consensus needs to be arrived if comparable research goals are to be met.

6 Investigation

Assessments are vital, necessary and sufficient to make a diagnosis of autism. No testing is needed for a diagnosis. Much to the chagrin of all concerned, we do not have the respectability of a confirmatory biomarker for validation of ASD. So, sadly enough, even in 2013, we do not need tests to confirm a diagnosis. However,

if any test aids in treatment, it should be performed whatever the cost and difficulty. For example, the American Association of Paediatrics (AAP) recommendation of chromosomal microarray analysis gives a yield of about 8 % of various genes involved. It is available in very few centres in the country like the CDFD and CCMB, though private laboratories would certainly welcome the recommendation. As research evolves and more specific recommendations become available, it would be useful to investigate along the lines of American recommendations. In a recent review, the recommendations of the AAA have been summarised and brought up to date several tests conducted on children as clinical have only academic relevance. It is better to learn from the experience of wealthier countries. In a recent review, recommendations of the past have been overturned because of the low yield of tests.

Tchacomas and Adesman (2013) have the following suggestions:

Genetic testing: CMA is suggested as the most robust of these tests. The AAP's autism tool kit recommends this test for every child with ASD. In our context, we can wait a while to learn from the experience of better endowed countries. As these tests do not detect Fragile X or Rett's syndrome, our policy should stay with these two tests when indicated by clinical features or family history.

Neuroimaging: MRIs are recommended only in acute regression, microcephaly, midline facial abnormalities, neurocutaneous lesions and confirmed neurological signs on clinical examination. Anyone who has witnessed the struggle of parents in sedating a child for diagnostic imaging would find relief in these recommendations.

Electoencephalograms are suggested only for those children who have clinical or suspected seizures, sudden regression or unexplained behavioural changes.

Metabolic testing: Testing should be conducted in children with failure to thrive, hypotonia, vomiting, lethargy, unusual odours, possibility of storage disorders and movement disorders. When indicated, tests would include renal and liver function, amino acids, pyruvate, lactate carnitine and acylcarnitine.

Blood lead would be indicted in children with pica. In children on antipsychotics, regular monitoring of lipid levels is necessary.

7 Treatment

"*Let me hold your shoulder like I used to when you started pointing and communicating she said trying to find a way. This time it was easy for the boy to write as he could feel the presence of the hand, his own hand linked to his body at the shoulder point where his mother was holding him. I have a concrete proof that to start with any new activity it is important for autistics like the boy, to be held at that part of the body which does the work as the relating ability develops slowly through practice. Then it can be faded out as the person gets the habit of that particular work*" (Mukhopadhyay 2003).

Tito again! Today many forms of therapy use the prompt offered by a gentle touch to help the child with autism master many fine motor skills like writing. The goals of treatment are twofold: to reduce disruptive behaviour and to increase communication and learning Treatment will depend on the age at the time of referral. The

different treatment options can be bewildering. Children need to receive a combination of psychoeducational approaches and medical interventions with family support. Assessment forms, checklists for history taking, assessment of regression, symptom checklist, age-based intervention recommendations, early psychosocial interventions and summaries of medication-related studies are included in the Indian Psychiatry Society guidelines for childhood and adolescent problems (Mukhopadhyay 2003). Effective early intervention (EI) programmes for children should provide an autism-specific curriculum content focusing on attention, compliance, imitation, language and social skills in a highly structured and supportive teaching environment with opportunities to generalise skills. The best interventions are the most intensive and focused. The best known behavioural programme is the applied behaviour analysis (ABA), which uses one-on-one interaction between the adult and the child. Another method is TEACCH which is a "whole life" approach aimed at supporting children, adolescents and adults with autism through the provision of "visual information, structure and predictability". Family support is essential and can help relieve the tremendous stress faced by parents of children with autism. The different treatment options can be bewildering. Children need to receive a combination of psychoeducational approaches and medical Interventions. Regarding new medical interventions, a technical expert panel has recommended that a child with ASD should receive comprehensive evaluation within 60 days of diagnosis, family concerns should be specifically addressed and 25 h of intervention per week is necessary (Naik 2007).

Seeking treatment: Help-seeking behaviour and EI have been underresearched.

Different reports exist as to when children comes for medical diagnosis. Reports vary as to the age at which self-referral takes place and diagnosis is made. There is an increased awareness about autism in the Indian Paediatric community, but for the most part, a lack of appropriate services is perceived as the main problem. Daley in 2004 studied the delay in reaching care (Maglione et al. 2012). The age of identification was less than 2 years in 83 % of patients in one centre, and less than 4 years in the remaining (Shivashankar and Satishchandra 1989). Conversely, another study showed a delay of 32 months between parents identifying a problem in the child's development and a diagnosis of autism being given to the child. Deviance or delay in speech was the main concern (Daley 2004). In a survey in Gujarat, 192 paediatricians expressed that barriers to early referral were insufficient time, lack of treatment choices and lack of knowledge regarding referral options (Chakrabarti 2009; Desai and Mohite 2011). This suggests proving more training and resources would help. In an update from the diasporas, a small study of eight South Asian parents, who were currently raising a child diagnosed with an ASD in Canada, barriers to diagnosis and treatment that were reported by parents were examined; 75 % of parents reported that they did not reveal their child's ASD diagnosis to their friends and their own family members, including their parents and siblings. Their most imperative needs were for information regarding services their child might receive in the future. (Grewal 2010). One study suggests that in the diaspora parents of children with ASD, outside the country cannot be considered as a single entity (Ravindran and Myers 2013).

Early Intervention in children with autism: When a child is younger, the brain has much more plasticity or ability to change and so changing or teaching new behaviour is much easier. Earlier studies showed that only half of all children with autism would

gain speaking abilities. Recognising and diagnosing autism before preschool age has been uncommon until the last few years. Listening carefully to caregivers as they voice their earliest concerns would facilitate early recognition (Singhi and Malhi 2001; Kishore and Basu 2011). Interesting new work has emphasised the earliest indicators of autism by following up high-risk "baby sibs" (Barbaro and Dissanayake 2013). In future, it is likely that autism will be diagnosed for most children in the toddler age period (18–30 months). Intervention should start as soon as characteristics of ASD are noted and continue for as long as required. When intervention starts early, children experience success and are more likely to engage socially and learn language and communication skills. Children are also less likely to become frustrated with a consequent decrease in challenging behaviours. Commencing working with the parents early in the therapeutic relationship can alleviate the distress. Anecdotal evidence of suicide in parents especially mothers abound. The importance o f psychological support and intervention with parents of ASD cannot be underestimated (Malhotra et al. 2002).

Learning (*DEALL*): One innovative Indian programme has been started in Bangalore by Karanth. The training for each child is based on the profile of the child and covers several developmental domains such as motor, communication, social and cognitive development. It also addresses other related issues such as eye contact, attention and sitting tolerance, compliance and behaviour. Ideally, enrolment to the DEALL program should take place by the age of 2.5–3 years. There should be a 1:4 staff: student ratio and therapy take place with 12 children per unit, 3 h per day/5 days a week. Training of trainers has also been initiated. Incidentally, Tito and Karanth felt she was a kind therapist from whom the boy benefitted (Karanth et al. 2010).

The Combined psychoeducational and biomedical approach: As part of an interventional programme, a combined psychoeducational and biomedical approach was used as an 18-month prospective, longitudinal, intervention study with 51 children with autism, aged one-and-a-half to six years, who fulfilled the DSM IV diagnostic criteria for autism with a developmental quotient (DQ) above 50 and normal gross motor milestones (walking by 15 months). The families had to be willing to follow a GF CF diet. Activities and intervention programmes were developed and tailor-made for each child depending on the level of functioning and development. The program was implemented on the basis of the TEACCH model. The TEACCH program was developed for children with autism at the University of North Carolina, Chapel Hill, in the 1960s and is popular worldwide. The TEACCH program involves structured teaching to train children and individuals with autism in the areas of social skills, communication skills, independent living skills, vocational skills and leisure skills. The diet was an elimination diet which was gluten-free, casein-free, sugar-free and preservative-free diet. Vitamin and mineral supplements were always provided. GI treatment was provided. Every patient was discussed individually with the child's paediatrician to monitor growth and nutrition. Children had free access to the paediatrician from the National Institute of Nutrition, who attended the hospital daily to discuss any dietary issues. Monitoring on a six-monthly basis on the CARS, PEP-R, REELS expressive, and REELS receptive scales was significant at ($p < 0.001$) on all four scales and on the overall developmental score. Both methods complemented each other. The biomedical approach helped the child pay attention to and benefit from

the individualised training programme. Parental stress scores came down considerably during treatment (Abbagani et al. 2011).

The Early Start Denver models (*ESDM*): A recent a clinical trial comparing ESDM with conventional autism therapy services randomly assigned 48 toddlers (aged 18–30 months) to receive either ESDM therapy or the EI services routinely available in their communities (Seattle). Both groups received roughly 20 h of weekly therapy for two years. Overall, those in the ESDM group showed greater increases in IQ, language and adaptive behaviour than children in the community-intervention group. This more typical pattern of brain activity was associated with improved social behaviour including improved eye contact and social communication (Dawson et al. 2012).

The Developmental, Individual, Relationship-based (*DIR*) *model*: The developmental, individual, relationship-based (DIR) model, designed by Stanley Greenspan in 1989, describes 6 milestones as crucial to a child's development. Parents and professionals involved with the child must comprehend how the milestones affect a child's emotional and intellectual growth. The six milestones are the following: self-regulation and interest, intimacy, two-way communication, complex communication, emotional ideas and emotional thinking. The major element of this approach entails that (a) professionals do floor time with the child, (b) parents observe floor time being done with their child and (c) parents change their style of relating to the child with regard to a given milestone. Floor time is a systematic way of working with a child with autism to help him or her. A study was conducted to establish the efficacy of floor time for the development of social behaviour in preschool children with ASD. The children who received intervention showed a qualitative change in their interactive behaviour (Lal and Chhabria 2013).

Social stories: *In a case–control study*, reading such stories and role playing led to significant improvement over controls in the RSSM rating scale for self-management (Lal and Ganesan 2011).

Sensory integration: In a qualitative study of 65 parents on sensory integration perception of mothers, it was found that the children were not averse to sensory integration, and this in turn encouraged participation (Joshi 2008).

Visual strategies: Objects, pictures, symbols and manual signs were used as visual tools with 14 one-on-one sessions; communication skills were considerably improved (Lal and Bali 2007).

Auditory processing methods: Common to both dyslexia and autism have been used to facilitate auditor communication (Sampath et al. 2010).

Coaching: Based on the premise that parents of children with autism have less positive experiences in parent–child interactions, parents were taught to break down tasks into achievable and objective components. This served to enhance a sense of mastery in the parent when goals were achieved (Raj and Kumar 2009).

Milieu therapy: The children who underwent intervention based on milieu approach showed an increased use of target language and functional communication skills across settings and conversational partners (Vishnu et al. 1992).

Parental Involvement Scale: In a pilot study at a Mumbai School using a Parental Involvement–Engagement Scale, it was found that higher parental involvement made for greater progress in emotional, social, language cognitive and motor skill development (Srivastava and Mukhopadhyay 2011).

The Lovaas method: Children below 6 years of age were treated at a Delhi hospital using parents as chief therapists. A mainly behavioural approach based on the Lovaas method was used. Parents were expected to spend at least 60–90 min per day training the child. A significant improvement was seen in DQ, the CARS and the ABC scores at the end of 8–30 months (Juneja et al. 2012).

Music therapy: Music therapy was used in children in an improvised interactive way to improve communication skills (Mukherjee 2008).

Yoga: The use of integrated approach to yoga therapy (IAYT) as a complementary therapy for children in a small study reported improvement in imitation skills and social and non-verbal communication (Radhakrishna 2010).

Several other techniques have been used, but have not been reported adequately in the Indian literature. These include speech therapy, cognitive behaviour therapy and sensory integration. Treatments based on traditional systems of Ayurveda and Yoga have emerged. They too need scientific validation. Music therapy is recommended as "a non-invasive, enjoyable and cost-effective therapy; unique outcomes are possible". Art as an EI tool has been described (Christopher 2011). Drama education and the use of masks have been used to improve social communication (Nelson 2011).

Augmentative Communication (*AC*): In one Mumbai-based study, 8 children received 12 sessions of language intervention using augmentative communication (AC); significant change was noted both in language and social behaviour (Lal 2010).

Picture Exchange Communication (*PEC*): The use of PECs in a 7-year-old male child was reported with 60 % improvement on several of the instruments used (Shahzadi Malhotra et al. 2010).

Assistive technology: Studying an emotional hearing aid-assistive technology, which enables children with autism to understand the facial expression of individuals in the social environment improvements, was reported (Nancy 2012).

Special care during other medical problems: A case report of a severe case of bruxism treated by dental intervention under anaesthesia was used to discuss the special patience and care needed in children with autism (Nagendra and Jayachandra 2012; Muthu and Prathibha 2008).

The best elements of many of these measures may be combined in a cost-effective manner and used even where optimum resources are lacking. In the Lovaas method, discrete trial training has gained popularity (Lovaas 2003).

7.1 Innovative and Emerging Treatments

Uncommon sense toys: Uncommon sense toys, being researched in Bangalore, encourage social interaction among children with autism. The toys have audiovisual and tactile feedback, which can be triggered by a child's action movement and voice. The toys help the child to engage in collaborative play through both individual responses and shared responses. Orientation, touch and expression are required to operate the three specifically designed toys (Dsouza et al. 2010).

Robotic technology: Robotic technology, appeals to children with ASD. This fact can be used to provide repeatable, accurate and individualised intervention services. In a study, a humanoid robot had its vision augmented by a network of cameras for

real-time head tracking using a distributed architecture. The robot could intelligently adapt itself in an individualised manner to generate prompts and reinforcements, based on the child's head movements to promote skills in social orienting. The system was validated for feasibility, accuracy and performance with six children with ASD, and a control group of six typically developing children (Welch et al. 2010).

Virtual environment: In another study of robotic technology using the same technique in children with ASD, a virtual environment has been designed where children with autism could participate in social activities with the social robots. Gaze and social distance are being studied as an initial step (Bekele et al. 2012).

Personalised learning: The authors propose a smart e-learning tutoring model for patients with ASD, with machine learning capabilities, which help in generating dynamic e-learning sessions and maximise learning opportunities through personalisation of the programme (Vullamparthi et al. 2011).

Ideas from other work New Ideas by Sinha: His first research on people with the disorder, in 2003, focused on the ability of children with ASD to integrate a visual scene. The autism literature is fuzzy on the subject, with some studies showing clear deficits and others showing none. Sinha believes he can help children with autism to achieve greater visual integration (Ostrovsky et al. 2009).

Drug development: Attempts are on to model proteins like Shank3, also known as proline-rich synapse-associated protein 2 (ProSAP2). ProSAP2 is a protein encoded by the SHANK3 gene which could be used for drug designing (Ostrovsky et al. 2009).

Animal studies: The role of green tea extract was studied in reversing behavioural changes induced by valproate and oxidative stress markers in mice. Both behavioural assessments and histopathological studies confirmed the usefulness of green tea extract (Mujawar et al. 2013).

7.2 Family Support and Community Support

Family support is essential and can help relieve the tremendous stress faced by parents of children with autism. Parent groups serve this purpose. Breaking the news can be a difficult procedure as many parents have heard of autism and cannot believe it is happening to them. Parents have a great need to know more about this problem, and nothing can substitute for time spent with the family. In a study in Goa, twenty interviews and nine focus group discussions were carried out with families of children with autism and with teachers and TD families. The key findings were the following: (1) raising a child with ASD places severe stress on the families with initial withdrawal, (2) personal and wider impact with discrimination, (3) parents respond well to supportive measures, (4) health education and religious sectors do not have awareness of these needs and (5) this study serves to identify the unmet needs of families with ASD (Banji et al. 2011).

Parental stress: Barua describes her own experiences of life with her son: the shock of the diagnosis, acceptance, unconditional love and affirmation (Barua 2007).

The Parenting Stress Index and brief psychological interventions: The PSI was used to assess stress among children with disability and autism with three-fourths of the group having significant stress. A qualitative analysis was further undertaken to evaluate the nature of these stresses. Even brief psychological interventions of 3–56

sessions addressing different issues like behavioural, supportive and educational techniques can ameliorate some of the emotional issues of parents of children with autism (John 2012). The importance of acceptance is stressed in the following account.

Community support: Kanner's case No. 1 stayed on in the community where he grew up. The community was proud of his abilities and protective.

"*Donald's neighbours not only shrug off his oddities, but openly admire his strengths—while taking a protective stance, with any outsider whose intentions toward Donald may not have been sufficiently spelled out. On three occasions, while talking with townspeople who know Donald, we were advised, in strikingly similar language each time:* "*If what you're doing hurts Don, I know where to find you.*" *We took the point: in Forest, Donald is* "*one of us.*" (Donovan and Zucker 2010)".

Staunch community support can certainly have beneficial effects.

7.3 Psychopharmacology

Medication should be used for targeted symptoms, in the smallest dose for the shortest period of time, keeping the side effects in mind. The question is sometimes asked as to why do not drugs work in autism "*Numerous studies have documented that autism stands out from almost all other psychiatric disorders in showing no marked benefits of psychotropic medication on core symptoms (such as impaired social reciprocity and social communication). Why? One possible implication is that the basic deficit does not involve neurotransmitters; if not, what does it involve? It is important to pose the question, not so much because of the implications for treatment today, but rather because a satisfactory answer could have important implications for the neural basis of autism. For the moment, medication is of some value for associated problems, but the enigma is why that seems to be all.*" (Jayarama and Bhat 2004; Buitelaar 2003).

Risperidone and aripiprazole have FDA approval. Effective for the target symptoms of irritability, they come with side effects which should be carefully monitored (Tchaconas and Adesman 2013). The parameters that need monitoring include blood glucose, lipids, liver function tests, prolactin and thyroid-stimulating hormone. Hyperactivity can be managed by methylphenidate and atomoxetine, though less successfully than in ADHD. Melatonin is effective in sleep issues; two new drugs hold promise, arbaclofen in Fragile X and an enzyme replacement proprietary combination, CM-AT (Tchaconas and Adesman 2013). Supplementation with omega-three fatty acids, nacyl cystiene and l carnosine have all been tested in RCTs and found useful. An Indian study replicated the usefulness of risperidone (Singhi Nagaraj et al. 2006). The use of donpezil in treating autism is reported as case study (Srivastava et al. 2011). However, there is serious concern that the core symptoms of autism seem to respond less readily to psychopharmacology, than in other psychiatric disorders. For a review of pharmacological treatment of ASD, practice guidelines may be useful, as also a more recent review (Mukhopadhyay 2003; Nazeer 2011).

7.4 Complementary and Alternative Therapies

Complementary and alternative therapies are defined as "a group of diverse medical and health care systems, practices and products that are not considered to be part of conventional medicine". They are called complementary when used together with conventional medicine and alternative when used instead of conventional treatment. In an extensive review of the subject, an interesting classification of treatments has been made. SECS stands for safe, easy, cheap and sensible; RUDE stands for risky, unrealistic, difficult and expensive. This method serves to categorise well-tested drugs as recommended, for example melatonin in sleep disorders and acceptable in conditions where costly or difficult or risky treatments do not get similarly categorised. This seems a useful tool for the clinicians as well (Lofthouse et al. 2012).

Complementary and Alternative Interventions as seen by social workers: A Czech student analysed attitudes of social workers to alternative treatment in Kerala. One response was stigma and fear of side effects in traditional medicine. Yoga was approved, but not Ayurveda; spiritual help was not recommended, whereas biological treatments were (Hudec 2012).

A Review of GFCF diets: New evidence suggests that a gluten-free (GF), casein-free (CF), or gluten- and casein-free diets (GFCF) can ameliorate core and peripheral symptoms and improve developmental outcome in some cases of autism spectrum conditions. The majority of published studies indicate statistically significant positive changes to symptom presentation following dietary intervention. Changes in communication, attention and hyperactivity are detailed (Whiteley et al. 2012). Specific characteristics of best and non-responders to intervention are not yet understood.

The Scan Brit RCT: The Scan Brit, randomised, controlled, single-blind study of a gluten- and casein-free dietary intervention for children with ASD assigned 72 Danish children to diet (A) or non-diet (B) groups by stratified randomisation. Data for 26 diet children and 29 controls demonstrated significant improvement in mean diet group scores on subdomains of the ADOS, the GARS and the ADHD-IV measures. Predefined statistical thresholds were surpassed in the GFCF group, so Group B was assigned to GFCF as well. At 24 months, while there was evidence of sustained clinical group improvements, there was a possible plateau effect for intervention in some cases at this point (Pennesi and Klein 2012).

Responders and non-responders to GFCF diets: Attempts have been made to study responders and non-responders to GFCF diets. In one questionnaire-based survey from 387 parents, the presence of GI symptoms, food allergy and sensitivities and strict diet implementation was indicative of greater improvement in ASD behaviours, physiological symptoms and social behaviours compared with children whose parents reported none of these symptoms (Whiteley et al. 2010).

The Chennai GFCF study: In a small study from Chennai of 50 children with autism, children on restricted diets showed improvement over a 2-month period in attention, sleep and reduction in hyperactivity and anxiety (Nazni et al. 2008).

Treatment of ASD has been the subject of intense research activity. While we can learn from the experience of others, consolidating proven useful measures and

scaling treatments is urgently needed. Drug treatment has not been as effective as in other psychiatric disorders and must be balanced carefully with monitoring of side effects. Certain complementary and alternative measures which are categorised as safe may be tried with parental consent.

8 Follow-up and Prognosis

> DONALD LIVES ALONE NOW, in the house where his parents raised him. FOR ALL THE PROGRESS that Donald has made in the decades since—the driving, the golfing—conversation is an art that continues to elude him. Except for once a month, that is, when he walks out the front door and leaves town. Perhaps the most remarkable aspect of Donald's life is that he grew up to be an avid traveller. He has been to Germany, Tunisia, Hungary, Dubai, Spain, Portugal, France, Bulgaria, and Colombia—some 36 foreign countries and 28 U.S. states in all, including Egypt three times, Istanbul five times, and Hawaii 17 times. He's notched one African safari, several cruises, and innumerable PGA tournaments.
>
> This is the same man whose favourite pastimes, as a boy, were spinning objects, spinning himself and rolling nonsense words around in his mouth. At the time, he seemed destined for a cramped, barren adulthood—possibly lived out behind the windows of a state institution. Instead, he learnt to golf, to drive, and to circumnavigate the globe—skills he first developed at the respective ages of 23, 27, and 36. In adulthood, Donald continued to branch out (Donovan and Zucker 2010).

Regular follow-up is required. Parents often shop for treatment, so ideally, all services can be offered in one setting, but this has been mostly difficult to achieve. With early and appropriate intervention, long-term outcomes have improved, and some children grow into self-sufficiency in adulthood, while several are able to function with support. The improvement in several children can be so remarkable that we need to adopt a more optimistic attitude. However, caution is needed in children with evidence of motor delay.

"Two factors that have been consistently associated with prognosis are language development and IQ. Very few children who have not developed some useful communicative speech by the age of 5–6 years have a positive outcome and, conversely, individuals who were either cognitively un-testable as children, or who had non-verbal scores below 50 were almost invariably reported as highly dependent. Best outcomes have been found for individuals with an IQ of at least 70 in childhood (Jayarama and Bhat 2004)".

Some years after presentation, older children around the age of 10 years to adolescence develop seizures unrelated to the severity of autism. In adults, affective disorders and obsessive compulsive behaviour are known to develop (Venkatesan 2005; Jayarama and Bhat 2004).

Optimal outcome individuals: In a study by Fein, at the University of Connecticut, several children lost their diagnosis of autism on all scales of assessment. These optimal outcome individuals ($n = 34$) were compared on standardised measures to age-, sex- and IQ-matched individuals with high-functioning autism ($n = 44$) or typical development (TD group, $n = 34$). The optimal outcome (OO) and TD groups' mean scores did not differ on socialisation, communication, face recognition or most language subscales, although three OO individuals showed below-average scores on

face recognition. Early in their development, the OO group displayed milder symptoms than the HFA group in the social domain, but had equally severe difficulties with communication and repetitive behaviours. These results substantiate the possibility of OO from autism spectrum disorders and demonstrate an overall level of functioning within normal limits for this group (Fein et al. 2013). In an Indian study, a single adult was followed up and showed inadequate social functioning (Chaudhari et al. 2008). In a small study, 33 of 37 children diagnosed as autistic disorder retained their diagnosis. Only 1 out of 6 children labelled PDD NOS retained the diagnosis. The follow-up was for about a year (Malhi and Singhi 2011).

9 Ethics

The main issue of ethics arise (a) at the patient and family level in using proven methods of treatment and (b) in maintaining confidentiality. As the use of Internet increases and parent groups stay in touch across the globe, it is important to be aware of new developments in the field and explain pros and cons of different remediable approaches, permitting parents to make informed choices. In a broader framework, it is necessary to protect Indian families and children from experimental use of new drugs, whose side effect profile is not yet fully understood. This is more the case when children cannot explain their discomforts. By and large, we have kept ourselves from being targeted for drug trials, but constant vigilance is necessary. Greater attention to ethical issues will enhance the quality of epidemiological, genetic and treatment studies (Daley et al. 2013).

10 Facilities

10.1 The Action for Autism (AFA)

An important development has been the formation of the AFA by Mrs Merry Barua. The AFA was started in 1991 to provide support and services to persons with autism and their families, and to create an environment in India, in which people with autism are able to grow to their full potential. The AFA is now the primary organisation in South Asia specialising in ASDs. The AFA is a non-profit organisation whose mission is to facilitate a barrier-free environment, empower families of individuals with ASD, act as a catalyst for change and build community responsibility for mainstreaming of all persons with ASD.[1] In a review of facilities available for children with autism and mental retardation, the models in use were special schools, inclusive schools, home-based education and units established by parent groups; 46.8 % preferred home-based education, 25.8 % were in special schools, and 19.4 % were in inclusive schools (Karnath Aluri and Karanth 2002). The educational support systems available to children with ASD have been reviewed elsewhere (Narayan et al. 2005).

[1] Action for Autism www.autism-india.org/afa.

Architecture: Architects too have shown interest in designing environments. It is possible to design better environments for children with autism by using tools like the researcher environment checklist (REC), teacher performance scale (TPS) and teacher environment rating checklist (TEC). Guidelines could be formulated for building design and landscaping to create the most conducive environment (Khare and Mullick 2008).

Organisations like the AFA can serve as an umbrella organisation to facilitate multicentre epidemiological studies, uniform assessment, early detection, intervention, follow-up and advocacy for children with autism. Already, the AFA has brought autism under the purview of the National Act for Persons with Disabilities and under the National Trust.

10.2 Government Initiatives

Services for persons with autism have been summarised by Bhargava as a report. She has summarised the details of several schemes available to persons with ASD (Bhargava 2010).[2, 3]

The National Trust: Setting up the National Trust for the Welfare of Persons with Autism, Cerebral Palsy, Mental Retardation and Multiple Disabilities Act, 1999, was an important step. The Act facilitates the realisation of equal opportunities, protection of rights and full participation of persons with disabilities and provision for appointment of legal guardian for persons with disabilities.

To promote inclusive school education, the following facilities have been created:

(a) Sarva Shiksha Abhiyan (SSA)

The key objective of SSA is Universalisation of Elementary Education (UEE), three important aspects of which are access, enrolment and retention of all children aged 6–14.

(b) Inclusive education for the disabled at secondary stage (IEDSS)

The IEDSS, launched in April 2009, provides assistance for the inclusive education of children with disabilities of Classes IX–XII including autism. Funds are provided for activities such as identification and assessment, assistive devices, allowance for transport, escorts, readers, uniforms, books and stationary.

(c) Capacity building of special teachers

Course curricula have been developed and standardised by the Rehabilitation Council of India (RCI) for (i) Diploma in Special Education (ASD) and (ii) B.Ed. in Special Education to handle the special needs of students with disabilities according to the National Trust in inclusive classrooms.

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[2] National Trust for the Welfare of Persons with Autism, Cerebral Palsy, Mental Retardation and Multiple Disabilities Act 44 of 1999. New Delhi.

[3] Persons with Disability Act. Government of India. Persons with disabilities (Equal opportunities, Protection of rights and Full participation), Act, 1995, New Delhi.

(d) Support for children with autism

The Central Board of Secondary Education (CBSE) has made several changes in the examination by-laws in February 2009 to help children with disabilities, including those with autism, giving the board (public) examinations of Class X and XII, which strengthen earlier relaxations.

(e) Other benefits

Health insurance, scholarships, income tax benefits to families, travel concessions, banking simplification and legal support have also been simplified.

10.3 The Role of NGOS

In a recent review, Patel has specifically called for the inclusion of MHNGOs as full partners of the government services in the National Mental Health Programme. Such a partnership could take several forms, including participation in committees to monitor the NMHP in each district, become providers of the DMHP services or provide community-based services like day care centres. NGO placements should become mandatory for psychiatric training, and NGO representation should be sought in all committees, planning at the state and national levels (Thara and Patel 2010).

11 Conclusion

In the past 70 years since the world became aware of autism, a great deal of scientific advance has taken place and information grown exponentially, but we still cannot see the woods for the trees. As a postgraduate student, one of my early seminars was on childhood autism and I believe my abiding interest in autism began in 1975. At that time, the incidence was reported to be 1:10,000–1:40,000 children. In 70 years, we have not improved on the inclusion criteria for diagnosis. Autism continues to be a disorder characterised by patterns of delay and deviance in the development of social and communicative skills with behavioural problems, often associated with exceptional skills, and arising in the first few years of life. Everything else about autism is a controversy. The name we call it by, the prevalence rate, the assessment, the aetiology, the investigation and treatment and of course prognosis. For every little step of progress comes a question. In 2013 comes the contradiction that the theory of a lack of neural connectivity noted on functional MRI may be an artefact caused by movement of the head. Some of these artefacts could be got rid off by "scrubbing", but the neural theories would need a rethinking (Deen and Pelphrey 2012; Wolff et al. 2012). We no longer blame parents for being cold and unemotional, but instead are confronted by an array of causative possibilities. Older fathers and migrant mothers have been implicated. Epigenetics is being given greater recognition in all branches of medicine. The interplay of several genes is now considered as aetiologically relevant. Every day brings new additions to the list of implied causative genes; a gene encoding a sodium proton

exchanger is a new entrant. Markers of inflammation are being increasingly identified with elevated levels of cytokines and transcription factors in children with autism. Earlier gold standards like the ADOS will now have to be revised in the light of DSM V. Along the way, we seem to have created and consolidated encapsulated areas in the gestalt of autism best exemplified by Insel's *Kingdoms*.

On 26 February 2013, Thomas R. Insel, Director NIMH, wrote on his blog that there appear to be Four Kingdoms of Autism.[4] He has hypothesised that the current perspectives on autism seem like four well-fortified kingdoms "each with its own truths. And each too often fails to understand or even recognize that their truths may not apply to all kingdoms". Much like Kipling's blind men of Hindostan, each was partly in the right.

(i) The *Illness* kingdom: Here, the search is for disease biomarkers to assist in diagnosis and molecular targets for drug treatments—and—eventually reduce the need for services.
(ii) The *Identity* kingdom: This supports adults who were once on the spectrum and now face problems in the "neurotypical" world rather than seeking to become "neurotypical", they advocate for acceptance or inclusion ("nothing about us without us") as well as recognition that autistic thinking may yield innovative solutions. As Temple Grandin asks rhetorically "Who do you think made the first stone spears?—The Asperger's guy. If you were to get rid of all the autism genetics, there would be no more Silicon Valley.[5]"
(iii) The *Injury* Kingdom: One of the more heated arguments surrounding autism has been on the possible role of vaccination and has led parents to feel betrayed by mainstream medicine who have then "turned to alternative treatments based on detoxification, diet, or oxidative stress. This kingdom advocates for prevention, recognising that identifying the cause is the most direct path to stopping the soaring prevalence of autism".
(iv) The *Insight* kingdom: These scientists use autism as s as an opportunity to study the social brain through procedures like mapping of the brain.

Insel rightly suggests that while all this work is going on, the most important activity would be for all concerned to work towards the goal of "ensuring that every person on the spectrum, irrespective of wealth, geography, or ethnicity, receives the best treatments and services". The best strategy to reunite the kingdoms is though proven efficacy of prevention and intervention. Every delay hurts some child somewhere and keeps some family in distress. This frantic pace of research, the evolving theories and the need for convergence of different disciplines emphasise the need for multicentre studies. In India, the most immediate research need is for epidemiological studies. These should be followed by training therapists in EI and best management practices. A parent body that would supervise and link collaborating agencies in a fund-efficient and cooperative manner seems the need of the hour. Much like

[4] Insel T, http://www.nimh.nih.gov/about/2013/the-four-ingdoms-of-autism.shtml. The four kingdoms of Autism Thomas Insel on February 26, 2013.

[5] Tedtalk TEDTalk 2010 Temple Grandin.

protocols are shared in several countries for diseases like cancer, an Indian consortium of interested medical and other professionals including basic scientists, educationists, psychologists, social workers, occupational and physiotherapists, speech and language specialists and dialecticians would save time, enhance the quality of research and prevent duplication. Using tried and tested methods would translate into meaningful patient and family care. To conclude, we are short of time, and we cannot wait another 70 years to solve all the mysteries of autism. Our time starts now.

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