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AUTISM SPECTRUM DISORDERS. Amara David G, Dawson Geraldine, Geschwind Daniel H (Eds.). Oxford University Press: Oxford, UK, 2011

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When I was first asked to review "Autism Spectrum Disorders," a text edited by David Amaral, Geraldine Dawson, and David Geschwind, I did not realize what a daunting task it might become. However, at 81 Chapters and some 1,400 pages, it has, in fact, been quite a challenge. At first I thought I would read a Chapter a day, making notes as I read. Alas, other obligations managed to intrude, and so it has taken me longer than I had planned originally. When I first began research in autism nearly 30 years ago, the field was much smaller, the issues fewer and simpler-seeming. While we have all enlarged our understanding and knowledge of pervasive developmental disabilities in the interim, any attempt on my part to do justice to every aspect of research and policy in this field would be unrealistic at best; and, hubristic at worst. Therefore, as there are Chapters in which I felt that I had little if any expertise to give a sensible opinion, I have avoided making comments in these areas.

Having made these caveats, the text is divided into 11 sections, ranging from historical aspects and developmental trajectories, to comorbidities and the broader behavioral phenotype, neurobiology and etiology, animal models, treatment, and public policy. It is encyclopedic in nature, and intended to be so, as many Oxford University Press texts are. Given my earlier remarks, I will not attempt to review all Chapters, but to provide brief comments on those in which I have either engaged in research, or believe have sufficient familiarity to make a reasonably thoughtful comment or two.

The Introduction and First Section provide an historical perspective on Kanner's original diagnosis published nearly 70 years ago, the changing classification of autism and pervasive developmental disabilities, and its subsequent effect on epidemiology and culture. The authors of the first two Chapters, Isabel Rapin and Michael Rutter, have more than a century's experience between them and related to the evolution of the field. A reading of both Chapters is therefore essential. In a somewhat controversial vein, Rutter remarks that empirical evidence regarding the efficacy of early and intensive psychological interventions on behavior are "thin," early claims by Lovaas [1987] notwithstanding. However, in an article not cited by Rutter, Smith et al. [2000] found both receptive and expressive language, as well as communication and socialization, do show significant improvements from baseline after 2 years training, as do toddlers in the recent study by Dawson et al. [2010]. In Chapter 3, Ami Klin presents a thoughtful and comprehensive discussion of Asperger's syndrome, including a history of its detection and diagnosis. In the following Chapter, Ozonoff and colleagues provide a useful discussion of patterns of regression and early onset, noting that early patterns are difficult to diagnose and that the mechanisms involved in each remain elusive. In Chapter 5, Zwaigenbaum suggests that diagnostic assessment can be made at a relatively early age using the M-CHAT, based on its initial respectable sensitivity and specificity. However, the current literature regarding the use of the M-CHAT for making such diagnoses indicate its sensitivity and specificity are moderate at best, especially given the variability in toddler behavior. Moreover, the positive and negative predictive values based on unrepresentative samples biases their predictive validity [cf. Fisch, 2012a].

Detection and diagnosis are essential features for estimating prevalence; and, in Chapter 6, Fombonne and colleagues list 48 such studies, beginning with Lotter's first epidemiological investigation in 1966. A less-than-critical examination of these prevalence data would suggest that autism has become an epidemic. However, on closer inspection, prevalence rates are found to shift upward as the criteria for autism changed or modified. There are other factors that have contributed to the increase, as Fombonne et al. also note. In Chapter 7, Grinker et al. attempt to account for differences in detection and prevalence as function of cultural variables, a cluster of factors which are often overlooked when comparing prevalence rates from epidemiological surveys. Patrick Bolton's commentary at the end of the section calls for the need of a valid and reliable scale for assessing autism and other pervasive developmental disabilities as a spectrum of disorder as opposed to the current nominal taxonomy of same (also see Fisch [2012b], for a more extensive discussion of nosology and prevalence in autism).

In Section II are presented the central features of autism and the respective behavioral trajectories as individuals age. The first Chapter in the section by Peter Mundy explores the assessment and modeling of social behavior in infants. A difficulty arises, however, when the neuro-cognitive model used is based on data derived from their testing instrument, the ESCS, which has no apparent psychometric features. Therefore, it may be that the ESCS does not reliably evaluate joint behaviors in which there are overlapping dimensions. In Chapter 10, Groen and Buitelaar examine the cognitive and neurological correlates of language in autism. However, the neural dysfunction based on evidence from speech and language assessments is weak and often contradictory. A particular sticking point for this reviewer was to have his point

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of view misrepresented, suggesting that autism was probably polygenic in origin [Fisch, 2008]. In fact, I proposed that autism was probably multi-monogenic in origin. In the next Chapter, Bodfish examines repetitive behavior as related to cognitive rather than neurobiological function. He suggests that repetitive behavior in autism is more like obsessive–compulsive behavior in terms of disruption in the basal ganglia and motor control. Chapter 12 examines developmental features and trajectories in infants and toddlers with an early diagnosis of autism. One of the arguments that the author, Rebecca Landa, puts forth is that the early diagnosis of autism, that is, one made before 30 months of age, is stable. In the next Chapter, Tony Charman examines development of autism in children between 3 and 5 years of age, and also comments that a diagnosis of autism appears to be stable in this group. On the other hand, high false positive rates were found by his group using the M-CHAT with toddlers [Baird et al., 2000]; and, diagnostic accuracy using the CARS in a sample of pre-schoolers was about 70% [Chlebowski et al., 2010]. To his credit, Charman concludes that heterogeneity in autism appears to increase with age and that predicting outcomes in this age group may prove problematic. In her Commentary at the end of Section II, Katherine Loveland, like Patrick Bolton, notes that the changing developmental features and behavioral heterogeneity argue in favor of a revision in our current classification scheme.

In Section III, co-morbidities associated with autism are presented in 13 Chapters. In Chapter 15, Dykens and Lense discuss the overlap of intellectual disabilities (ID) that exists in most individuals diagnosed with autism. Of 14 prevalence studies presented in their Table 15-2, the proportion of ID ranges from 34% to 84%, the median for which is about two-thirds. With such a wide range in proportions, it is difficult to understand how some of these studies could be representative samples of the autism population. The authors recognize this concern, and cite as problematic those studies which truncate their sampling at lower IQ levels.

Section IV is comprised of chapters devoted to the broader autism phenotype (BAP). One of the concerns raised by Losh et al. is that the "BAP remains a poorly understood construct." As there is no consensus regarding the BAP, research in this area must continue to be a challenge. One such are the scales presumed to measure the phenotype. Should BAP be considered a clinical disorder to be included in DSM? Losh et al. discuss these issues at length. Biological aspects of the BAP, as presented in Chapter 28, are inconclusive with regard to brain structure. Appendix B to the Chapter presents a useful summary of the literature for possible biological markers. In Chapter 29, Constantino discusses autism as a unidimensional quantitative entity rather than a triad of qualitative impairments. To illustrate the point, the author presents figures of scores from the SRS scale to assess autism, noting cut-points that differentiate affected from unaffected males and females. A single-factor structure has its appeal, particularly if one conceives of autism spectrum disorders as a unidimensional disability. However, it does not examine differing degrees of severity in each of the three areas of impairment: Socialization; Communication; and repetitive/bizarre interests. And, of course, the decision as to where to draw the cutoff may be found by ROC analysis, but that presumes that individuals recruited for the study are representative of the population and not merely a sample of convenience. In their Commentary for the section, Parr et al. recapitulate the problems associated with research in BAP: the variability in the phenotype; the lack of a firm biological marker; and, the determination as to the location of the threshold between affected and unaffected individuals.

Section V fleshes out the known neurobiology associated with autism; and, in Chapter 30, John Rubenstein presents an overview of the various genes and genetic abnormalities found in individuals with autism. He notes how multiple monogenetic abnormalities in complex neural networks can have a cascading effect in brain, producing some form of pervasive developmental disorder thereby. In Chapter 35, Courchesne and colleagues note atypical brain development in infants and toddlers who eventually develop autism; and, that changes in brain size, weight, and volume from birth to adulthood could account for the abnormal behavior observed in autism. In a similar vein, Minshew et al. argue persuasively in Chapter 36 that the current paradigm focuses incorrectly on autism as a neurobehavioral disorder. Instead, it should shift, and that we view autism as a neurobiological disorder instead. In the section Commentary, Pat Levitt suggests further that a "moratorium" on animal models for autism be imposed until a better understanding of how social behaviors evolve can be determined. This cautionary note will moderate the discussion on animal models in a later section.

The genetics of autism is expounded in Section VI. In her presentation, Janine Lamb suggests that, based on recent studies, genomewide screens for autism appear to have limited utility given their lack of reproducibility. Furthermore, the genetics of autism may well be multi-monogenic. In Chapter 40, Judith Miles examines the quest for subgroups in autism resulting from differing degrees of severity in the triad of dysfunction. There is also consideration of the possible differences between phenotypes and endophenotypes. However, until biomarkers are found that discriminate between the two, the fuzzy boundary between the two types will remain controversial. In the following Chapter, Kaymakçalan and State note the recent developments in technology that have allowed researchers to identify genetic aberrations more rapidly and precisely, for example, copy number variants, in their search for causes of autism; and, they observe the growing evidence to suggest that single gene abnormalities can produce more than one neurobehavioral disorder. In his Commentary at the end of the Section, Daniel Geschwind notes that the various genes that have been identified and associated with autism have diverse biological functions, leading him to conclude that autism is probably a neural network problem; and, that the effects of environment may interact with genetic variants in a stochastic fashion, producing autism or autism-like behaviors as a result.

Section VII is the most terse, and probably for good reason. Other than what had been observed regarding infections during pregnancy, not much new in the way of environmental causes has been discovered. Chapter 47, by Hertz-Picciottto, discusses large epidemiological studies and spends a fair amount of space providing a balanced perspective of the MMR controversy and the putative association between vaccines and autism. For this reviewer, the retraction by the Lancet [Editors of The Lancet, 2010] of the article by Wakefield et al. [1998] speaks volumes.

Animal models and theoretical perspectives are examined in Section VIII. In the chapters I read, all authors begin with a caveat concerning animal models of human behavior, invoking three criteria by which a reasonable model should be established: face

validity, construct validity, and predictive validity; to which I would add, discriminant validity. Blaker-Lee and colleagues consider the zebrafish, not so much a model as a tool to study autism, by examining genetic homologs of human autism; and, that these genes perform orthologous functions in both species. In Chapter 51, Yang et al. reflect on mouse models of autism. At the outset, they note that neither construct validity nor predictive validity is currently feasible with murine models, thus limiting the utility of the prototype. They discuss at length lab techniques by which to evaluate deficits in socialization and communication in the behavioral phenotype, both of which are essential in developing a satisfactory mouse model. These concerns are echoed in the next chapter written by Hsiao et al. Chapter 53, by Bauman and Amaral, highlight the ethical and other issues in developing nonhuman primate models of autism. As our nearest biological relatives, nonhuman primates offer many advantages over murine and zebrafish models. However, devising means by which to introduce autism in primates is problematic, as these authors discuss.

The final section I shall review concerns treatment approaches. Since autism and autism-related disorders are neurobiological in nature, unless the underlying neurological features are somehow ameliorated, autism must remain a lifetime disorder. In their two chapters, Tristram Smith and Laura Schreibman comment on the use of applied behavior analysis (ABA) in different settings with children diagnosed as autistic or autistic-like, the technique later reiterated in Chapter 61, which is devoted to infants and toddlers. To the extent that it has been successful, ABA is implemented at an early age, identifying target behaviors for modification, and requiring intensive, long-term training. The methodology is not without its critics (see earlier comments by Rutter) and outcome measures such as IQ scores have been criticized as well. However, recent studies, for example, Dawson et al. [2010], Sallows and Graupner [2005], found significant improvement in language, communication, and socialization skills in the groups they treated. In Chapter 60, Greenspan and Wieder offer a different model based developmental, emotional and relational aspects of behavior. Unfortunately, the chapter lacks the kind of empirical evidence that would suggest the model is valid and useful.

In summary, ''Autism Spectrum Disorders'' is an important, comprehensive text devoted to all aspects of research and policy involving autism and autism-like behaviors, and is a must for anyone who does research in these areas.

EDITOR'S NOTE

The following two Book Reviews by Dr. Fisch deal with recently published comprehensive texts on the autism spectrum disorders (ASDs). I would like to turn the reader's attention to other recent related articles on ASDs in the Journal: During 2012 the Journal devoted an entire issue of AJMG Part C, Seminars, called: Autism and Intellectual Disability: Two Sides of the Same Coin'' on this topic. In the May AJMG Part A, Dr. Fisch reviewed issues on ASDS in his Commentary. These articles can be access freely on the AJMG Wiley Interscience web page.

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