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State of the Science in Autism: Report to the National Institutes of Health[1]

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New findings of the mechanisms underlying other developmental disorders such as fragile X syndrome and insulin-dependent diabetes mellitus led to an intensive lobby by parents of children with autism for similar advances in the study of autism. On April 10 and 11, 1995, the National Institutes of Health (NIH), in response to a Congressional request, assembled a working group of distinguished scientists at the NIH to assess the state of the science in autism, identify gaps in knowledge, and make recommendations to the NIH regarding promising areas for future research. Researchers in autism and related areas; representatives of the Autism Society of America; the Autism National Committee; and invited consultants contributed to the discussions reflected in this report.

Follow-up sessions were held at the national conferences of the Autism Society of America and the Autism National Committee. Thoughtful comments on the preliminary draft of this report were received from the April conference participants, at the follow-up parent conferences, and over a 4-month period from other professionals, parents, and self-advocates. Scientists listed as authors of the Report chaired one or more of the conference sessions. Major presentations at the conferences are summarized in the individual papers that follow the Report.

The NIH and follow-up conferences were cosponsored by the National Institute of Child Health and Human Development (NICHD), the National Institute on Deafness and Other Communication Disorders (NIDCD), the National Institute of Mental Health (NIMH), and the National Institute of Neurological Disorders and Stroke (NINDS). In keeping with the Congressional mandate, questions of interest to the NIH formed the basis for the conference and served as the framework for this report. These questions were developed by the NIH Inter-Institute Autism Conference Coordinating Committee: Duane Alexander (NICHD), conference convener; Judith Cooper (NIDCD); Felix de la Cruz (NICHD); Peter Jensen (NIMH); Marie Bristol (NICHD), Chair; Rebecca del Carmen (NIMH); Ralph Nitkin (NICHD); and Giovanna Spinella (NINDS).

DIAGNOSIS

C. Lord

Response to NIH Questions

Question 1: Is there a universally accepted definition of autism? Is there sufficient scientific evidence to support this current definition of autism spectrum disorders as separate from other developmental disorders? For the first

time, there are consistent criteria for diagnosis of autism spectrum disorders in both DSM-IV (American Psychiatric Association, 1994) and ICD-10 (International Classification of Diseases, 10th ed., World Health Organization, 1993). The working group agreed that there is both national and international support for these newly published definitions. The precision of these definitions will continue to evolve as new research clarifies the phenotype (visible characteristics of autism). Identification of one or more biological markers for autism disorders is needed to diagnose definitely atypical cases. Strong empirical support in the DSM-IV international Field Trials and other NIH-funded research, however, indicates that *the clinical diagnosis of autism remains one of the most reliable diagnoses in psychiatric or developmental research*. Additional research is needed to establish the validity of the diagnosis in terms of criteria based on etiology, course, and response to treatment.

Definitions of Rett syndrome (RS) and childhood disintegrative disorder (CDD) also yielded clear, consistent differences from Autism (A) and from other disorders in the DSM-IV Field Trials (cf. Volkmar, following paper) and in other studies. Current definitions appear adequate for estimates of the incidence and prevalence of these disorders in the United States. The new definition of Asperger syndrome (AS) makes the distinction between A and AS clear and so provides the first opportunity to assess the incidence and prevalence of AS separate from A. A category such as Pervasive Developmental Disorder–Not Otherwise Specified (PDD-NOS) is still needed, but would be more appropriately entitled "Atypical Autism" for cases that meet some, but not all of the criteria for autism. Standard measures that yield these diagnoses across the age span from 3 years to adulthood are now available and used widely in research in North America and Europe.

Question 2: How do the characteristics of autism, Asperger syndrome, Rett syndrome, and childhood disintegrative disorder change with development? There are a number of studies in which characteristics of A, RS, and CDD are compared in different age groups of children, adolescents, and/or adults (i.e., cross-sectional studies). However, there are few studies following the same children as they age so we have little evidence of how individuals actually change across the life-span (i.e., longitudinal studies). Asperger syndrome is a term that has been used frequently with adolescents and adults rather than with young children, so we have few cross-sectional *or* longitudinal data on AS.

Several relatively large-scale, high quality, follow-up studies exist of psychometric (mental measurement test) data for autistic individuals. These studies have shown that the diagnosis of autism continues to apply as the children age and change, even after they have developed language. Longi-

tudinal data are needed for all autism spectrum disorders in order to trace individuals' paths of development. Such data would enable us to define the course of the disorders, to aid in projecting clinical outcomes, and to plan for clinical intervention at various ages.

Question 3: What other disorders that occur as separate disorders in conjunction with autism (comorbid conditions) must be taken into account in the diagnosis and assessment of autism, Asperger syndrome, Rett syndrome, and childhood disintegrative disorder? Most, but not all persons with A also have some degree of mental retardation. There is now a very clear expectation in behavioral research that degree of mental retardation and severity of language deficit must be considered in designing and interpreting studies of the autism spectrum disorders. These co-occurring factors (mental retardation and degree of language deficit) have received less consideration in biomedical research. Lack of control for mental retardation and language deficits may be one reason why the replication rate of findings (i.e., multiple investigators obtaining the same findings) within biomedical research has typically been much lower than within behavioral research. The importance of diagnosis of comorbid (co-occurring) conditions such as affective disorder (e.g., depression) or obsessive-compulsive disorder, particularly in adults with autism spectrum disorders is also recognized, but standard procedures to do so are not well established. These await further research. It is particularly important to clarify the difference between true comorbidity and other ways in which symptoms from autism and different disorders may overlap.

Question 4: What additional research in autism, its related conditions, or relevant normative behaviors is needed to clarify subgroups in this heterogeneous population? Many investigators have proposed different subgroups in autism and these differ depending upon the theory that the particular research group espouses about the cause and/or central deficit in autism (e.g., language, motor problems, immune and/or serotonergic system differences). However, often the neurobiological or other feature purported to differentiate between or among subgroups is itself of questionable reliability. Studies of subgroups are important, but are premature if they are conducted using approaches that are not reliable or well established. One or more biological markers (e.g., genetic or neurochemical) is urgently needed to distinguish autism from other disorders and to distinguish subgroups within the autism spectrum disorders.

Recommendations of the Working Group on Diagnosis

1. Use of standard diagnostic procedures that operationalize (specify for research) DSM-IV/ICD-10 criteria is needed to promote communication

among scientists, clinicians, and parents, and replicability across studies. Diagnoses are not being made consistently in clinical or research settings.

2. Identification of individuals with AS and the investigation of external factors that validate the distinction between AS and A, and between AS and related learning disabilities is a high priority as well as investigation of the distinctions between severe autism and severe/profound mental retardation.

3. A central registry of persons with CDD is needed to enable researchers to find enough well-defined cases for the scientific study of CDD and for clinical information purposes. A standard protocol for clinical investigations of children with disintegrative disorders is also needed.

4. Longitudinal studies are crucial in order to provide data concerning differences and similarities in the individual developmental patterns (trajectories) of children with autism, particularly for the highest functioning individuals whose accomplishments may have been underestimated.

5. Establishing diagnostic criteria for very young (under age 3) children with autism is an urgent priority. The national trend away from specific diagnoses for young children in favor of generic terms such as "developmentally delayed" will result in a lack of appropriate early intervention services for children with autism. Continued development of reliable screening as well as diagnostic instruments is a critical need.

6. Studies that allow more accurate description of adults with autism, particularly those that address issues in the transition from school to work, are a high priority.

7. To be useful, studies of subgroups must be hypothesis driven (i.e., address a specific research question) and must validate subgroups using reliable, well-established measures that are not part of the diagnostic features.

8. Studies of subgroups that have been replicated across independent centers and across time, and those that address significant aspects of diagnosis such as course, response to treatment and well-defined levels of etiology (causes), pathophysiology (mechanism of structural and functional changes), and behavioral repertoire are a high priority. Studies of sex differences in autism are also clearly needed.

9. Minimum standards for comparison groups in studies of autism include comparability on mental handicap, degree of language impairment, and comorbidity (co-occurrence) of other conditions.

10. In studies of comorbidity of other disorders such as depression or obsessive-compulsive disorder, there is an urgent need to develop standard, reliable procedures for diagnosis of such disorders in individuals with autism, particularly in those with insufficient verbal skills for typical methods to be employed.

11. Research is urgently needed to assess the following interrelated questions: (a) Does having autism and another disorder change the nature and particularly the response to treatment of the comorbid disorders? (b) Are persons with autism more at risk than other people for certain other disorders? (c) Are there symptoms or other disorders not currently included in the phenotype of autism that are so common in autism that they might better be considered part of autism, for example, certain movement disorders?

EPIDEMIOLOGY

E. J. Costello

Epidemiology is the branch of medical science that deals with the incidence, distribution, and control of disease in a population (Webster's). *Prevalence* refers to the rate of the disorder present in the population at a given point in time. *Incidence* refers to the number of new cases occurring in the population during a given period.

Response to NIH Questions

Question 1: What is the best, empirically substantiated estimate of the prevalence of autism spectrum disorders in children and adults in the United States, and in other countries? There are no prevalence estimates specifically for the United States, but recent studies from Canada and from Japan indicate that autism is not a rare disorder. Both studies found prevalence rates of autism greater than 10 per 10,000. However, these studies used fairly small (<100,000) samples, and the confidence limits are wide (±5 per 10,000). A rate of at least 22 per 10,000 has been estimated for the broader autism spectrum disorders. Because of similarities between the United States and Canada, the Canadian data are likely to be reasonable estimates of prevalence in the United States for most purposes. Given the available data, there is little justification for the potential costs of a national prevalence study of autism in the United States merely to estimate the prevalence of autism spectrum disorders. Money would be better spent on developmental risk-assessment or cost-benefit studies.

Question 2: What efforts are currently underway to improve estimates of prevalence of autism in children? How can these studies as planned, or with modification, answer the Congressional question regarding prevalence in the United States? There are a few studies of the prevalence of childhood disorders underway or in the planning stage. It is possible that autism could

be included in one or more of these studies. The difficulties of doing so are formidable.

There are two main approaches to obtain prevalence estimates of autism: population-based studies (finding persons with autism in the whole number of people in a country or region), or studies of treated populations (finding the number of persons with autism in the populations of treatment settings such as hospitals, clinics, special education settings). Population-based studies provide unbiased samples since everyone is potentially included, but require very large samples to identify reasonable estimates of disorders like autism (e.g., 500–1,000 households would have to be surveyed to identify 1 child with autism). It is estimated that a sample of over 100,000 children would be needed to produce reliable estimates of the prevalence of autism with greater precision than is currently available in the international epidemiologic literature. Children with autism could be counted in smaller treatment-based studies since they are usually referred for services. However, problems include the following: (a) it is difficult to be certain you have found all treatment settings; (b) not all settings will be willing to participate; and (c) well-functioning children will be underestimated since they may not be served in the special treatment settings. The NIMH has recently funded a network of university sites to conduct epidemiologic research on childhood disorders. This network of centers, called UNOC-CAP will study the *U*se, *N*eed, *O*utcomes, and *C*ost of *C*hild and *A*dolescent *P*opulations. Both population-based and treated-sample studies will be carried out in UNOC-CAP and specific diagnostic measures will be included. These sites are already funded and procedures specific to the screening and diagnosis of complex disorders in children have been developed.

The National Health Interview Survey is too small to yield valid national estimates of autism. It also uses lay interviewers who may have difficulty in administering a respondent-based interview to identify a disorder like autism. The only U.S. study other than UNOC-CAP known to use diagnostic measures, the Project on Human Development in Chicago neighborhoods, is also too small and geographically too localized. Other ongoing national surveys are too small, do not include the relevant information, or could not be adapted easily to identify autism reliably.

Question 3: What contributions can epidemiologic research make to understanding the etiology, and/or treatment of autism spectrum disorders? Knowing how many and where cases of a disorder occur in the population (*descriptive epidemiology*) is useful for assessing: (a) the number of individuals and families affected by a problem; (b) the size of the financial costs to be expected; (c) the relative cost burden to families, states, and the federal government, or to different service agencies (e.g., education, health, child welfare, juvenile justice); (d) the distribution of the cost and need for serv-

ices in various geographic, ethnic, or socioeconomic groups; (e) the rise and fall in rates of the disorder over time, and, potentially, the impact of new social policies and treatments on prevalence and outcomes.

Some of the most powerful uses of epidemiology in medicine are as an analytic methodology, that is, as a way of testing hypotheses about causes of disease and the consequences of prevention or treatment strategies. The working group believes that *analytic epidemiology* can make important contributions to improving understanding of etiology, diagnosis, and treatment.

Etiology. Genetic epidemiology has already shown its importance for understanding etiology, and this importance will grow, not only as more genes are identified but as the functional roles of those genes are understood developmentally. Preventive interventions have to be based on etiologic theory; thus every intervention study is an implicit test of theory. Descriptive epidemiology can provide the basic hypotheses for interventions, as well as the methodology for testing the theory.

Diagnosis. The process of turning a taxonomy such as DSM-IV into instruments for epidemiologic studies helps to tighten the diagnostic criteria, making them more reliable for both epidemiologic and clinical purposes. The process of developing screening instruments helps to refine diagnosis by identifying the core symptoms and the range of variability of the diagnosis. Developmental epidemiology helps to track the developmental sequencing of patterns of symptoms and the impact of symptoms at one time on functioning at a later stage. Longitudinal studies also help to identify the development of compensatory strategies to cope with earlier symptoms.

Treatment. In an epidemiologic context, every treatment is an experiment, testing the validity of a causal theory. Clinical epidemiology, a highly developed aspect of research in many areas of medicine, has hardly gained a foothold yet in psychiatry or child development, but can provide a framework for comparing the cost-effectiveness of various treatment approaches, and examining the outcome of treatment trials for what they say about the causes of disorder and functional impairment.

Recommendations of the Working Group on Epidemiology

1. The Canadian data on prevalence are adequate for most U.S. uses. Rather than funding a national prevalence study of autism, autism should be included as one of the childhood disorders in the screening stage of the NIMH UNOC-CAP studies. A follow-up of all potential cases could then be done through UNOC-CAP with a more intensive evaluation, perhaps using experienced clinicians and one of the standard assessment packages currently in use in autism research. The UNOC-CAP population sample will not ex-

ceed 20,000 in all, but can establish rates of autism spectrum disorders for the general population. It will be too small to produce reliable rates for minority populations or to allow comparisons of stable rates for different age groups. The treated samples will not exceed 4,000, and are likely to yield localized rather than national estimates. However, the data from UNOC-CAP would provide significant, cost-effective additions to current U.S. information on autism, particularly since prevalence data will be collected in the context of service use and need, cost, and treatment outcome.

2. Research should be implemented to address the following issues: (a) Variations in the longitudinal course of autism, from early childhood into adulthood: Why do some children do well and some poorly? (b) "Boundary conditions" around autism: What is the rate of strictly defined autism relative to the rates of other types of pervasive developmental disorders, and learning disabilities? (c) Patterns of autism-like deficits in families of children or adults with autism: What is the prevalence of these problems? (d) At what age do children who will develop autism become identifiable? (e) Sociodemographic correlates of autism: What are they? (f) What other disorders (e.g., seizures, depression) may occur during different developmental stages and in which subgroups in autism? (g) Costs associated with the appropriate treatment of children with autism: What are the costs associated with different types of lifetime support of persons with autism and their families? The working group believes that these issues can best be addressed in developmentally focused, longitudinal epidemiologic studies that follow families over time. Such studies need to include not only the child but also the family.

3. There was support in the working group for a national autism registry. Registries have proved to be invaluable tools in clinical epidemiology. Such registries have been very useful in some other branches of medicine (e.g., tumor registries, birth defect registries).

PATHOPHYSIOLOGY OF AUTISM: ETIOLOGY AND BRAIN MECHANISMS

ETIOLOGY

M. A. Spence

Response to NIH Questions

Question 1: What is the appropriate framework for studying autism? Are there multiple genetic loci and would this present insurmountable obstacles to

research? The consensus is that there must be heterogeneity (different genes being responsible in different families) within the autism spectrum disorders and this will undoubtedly make the search for etiologic factors more difficult. However, the goal is obtainable. Even if numerous loci contribute to autism and the sibling relative risk is therefore much lower than reported, it would take possibly 400 sib pairs and 300–400 marker loci to map the gene. That is a sample which could be achieved with international cooperation and an NIH-directed effort.

Question 2: Are there genetic models and/or genetic techniques that have been used successfully with other developmental disorders that may be applicable to autism? Family studies of affected pairs of relatives is definitely the method of choice for the time being as it avoids having to workup and classify borderline and problematic cases. Actually locating the responsible genetic loci after mapping to a general gene region is a *very difficult* task. This work would be aided by association tests and linkage disequilibrium and therefore these tests are also applicable but must be applied in special populations to be most informative. It is essential any time family data are collected to consider, ahead of time, the restrictions imposed by genetic methodology and whenever possible take those into account when designing the studies. Epidemiology has provided sufficiently accurate estimates of the prevalence for the genetic analyses but also contributes by providing quality data on subtypes and comorbid conditions. Note also the query under Unresolved Issues regarding evaluating the need for a large twin study. (See recommendations for specific research below.)

Question 3: Do genetic and environmental factors act through common mechanisms to trigger the pathophysiology associated with autism? It is not premature to investigate gene–environment interactions. In fact, there was a strong consensus at the meeting that there must be relevant environmental factors even in the face of the genetic evidence. Even monozygotic (MZ, identical) twin pairs are not always concordant for autism (do not both always have or not have autism). Immune irregularities also suggest a role for pathogens, and findings of minor physical anomalies suggest a delay or disruption in early development. Given the complexity of autism from a clinical neurologic perspective, it appears highly likely that there is a common pathophysiologic sequence that is triggered in various ways by epigenetic and/or environmental factors. Clear identification of subtypes and rigorous studies on defining comorbid conditions will be a major first step in research in this area. Longitudinal studies are also an essential means of obtaining critical information regarding gene–environment interactions. Additional research on environmental causes or precipitants is clearly warranted.

The natural course of the autism spectrum disorders and the early predictors of later diagnosis are not yet well identified and understood. There

is a sense that studies in these areas are making progress and should be encouraged for a variety of reasons. An important contribution of these studies will be a better understanding of the developmental stages and critical times in the course of the disorders. This will be invaluable in understanding gene–environment interactions.

Question 4: How can the genetic basis for autism be confirmed and further identified? We are definitely ready to test gene linkage hypotheses by initiating a formal genome search focused primarily on multiplex families (see below). However, there is no reason why these genetic family studies could not also serve as the primary vehicle for obtaining all the essential clinical and treatment data possible on the affected individuals and common relevant variables on the relatives. This procedure would avoid the expense of mounting both genetic and other studies and also improve measurably the quality of the genetic analyses. This multidisciplinary approach is exactly the one that has proven so effective in other complex diseases (such as breast cancer) which have seen quantum leaps in knowledge in the past couple of years.

Recommendations of the Working Group on Etiology

The search for the etiology (underlying causes) of the autism spectrum disorders is intertwined with research on diagnosis, pathophysiology, and treatment. Information from each of these areas helps to point the way toward possible causes. In turn, each of these other areas awaits discovery of the biological marker(s) for autism needed to expand and confirm its own findings. The working group on etiology recommends the following research priorities.

1. Genetic Analyses. There was remarkable consensus at the meeting that autism is a genetic condition. Mapping studies should be undertaken to identify the genetic loci that contribute directly to the disorder. The familial relative risks are sufficiently large to indicate the action of genetic factors and estimates of the number of loci involved are on the order of 3–6. For those reasons it was suggested that studies be initiated using affected pairs of relatives methodology (probably sib pairs, i.e., pairs of siblings). The information from the Human Genome Project, namely, the human fine-resolution genetic map, is exactly the required information to plan and carry out a successful genome search for loci contributing to the autism spectrum disorders. In addition, the parallel development of designated experimental organism maps and their sequencing will also contribute if/when appropriate animal models for specific aspects of the spectrum are developed. However, there are several important concerns and issues to be addressed if this research is to be sufficiently rigorous to have a rea-

sonable chance of success, especially in view of the expected genetic heterogeneity (different genes being responsible in different families): (a) A very strictly applied set of diagnostic and sociodemographic criteria is essential in selecting individuals for these studies. Research on standardization of screening and diagnostic techniques and definitions of subtypes is directly relevant here. (b) The best strategy for ascertainment (identification of subjects) is to focus on multiplex families (more than one affected individual in the same family who independently meet criteria for diagnosis) to minimize the problems with uncertain or borderline cases. (c) From the beginning, the available sample should be split into two subsamples, one for detecting the loci and another for validating the results. These families are sufficiently rare that if most are inadvertently used to detect the linkage it will not be possible to confirm the results without an undue time delay. (d) Careful consideration must be given to the design of the study because of the vast amount of work necessary to have sufficient genetic markers to complete a thorough genome search (which is required in the absence of good candidate genes). Therefore, the design will need to carefully weigh the three points above as well as the possibility of collecting parents and single cases (trios) for haplotype relative risk analyses which will be essential in finding the specific loci responsible after identifying a region of the genome through linkage analyses.

2. Family Studies. It is important to emphasize that studies of family members have roles in addition to the linkage studies discussed above. For example, the gender ratio difference in autism is striking and families of females with autism may provide clues for understanding this difference if carefully studied. The following are other possibilities, but not an exhaustive list: (a) Geneticists should be included in planning any family studies since some (not all) of the more rigorous genetic analyses require that families be identified in a manner that can be specified in the likelihood equations. This ascertainment must be defined *before* the families are selected for study. By including this prior planning, families will be eligible for inclusion in the genetic studies as well as providing data for other purposes. (b) Family studies provide a unique opportunity to test whether or not the defined subtypes (e.g., clinical, drug response, language acquisition) also point to detectable differences in siblings and parents, recurrence risk (genetic subgroups), or other important features. Several areas of research, including neurochemistry and language studies, already have data indicating that some but not all families have nonautistic members who also display detectable differences when studied.

3. Epidemiological Studies. Current estimates of prevalence of autism are sufficient for the genetic analyses and no further precision is required at this time. However, the epidemiology approach would provide invaluable

information in the definition of subtypes, comorbid conditions, and documentation of the range of variable expression of all of the spectrum disorders through the correct sampling and statistical analyses of the required data. Possible environmental causes or precipitants of autism may also be revealed. UNOC-CAP data would be useful in this regard.

4. Statistical Issues. Throughout the conference, there were discussions about the need for statistical rigor in diagnosis, defining subtypes, identifying risk factors, designing studies, and determining sample sizes. All the points raised are essential for the quality of the data and directly affect the genetic studies. These issues are discussed elsewhere in the report (cf. Statistics below), but should also be considered in any discussion of genetics.

5. Animal Models. Research in animal models, as with all good research, should be hypothesis driven (i.e., designed to answer a specific, testable question). However, there are now several good reasons why time should be spent considering appropriate animal models with the possibility of using them to move the research forward more quickly. For many of the biological variables, and quite possibly for the behavioral variables (such as cognition), study in animal models permits rapid breeding schemes which lead directly to estimates of heritability and number of involved loci. Added to that now is the direct comparability of the genetic maps among organisms (e.g., mouse and man) which facilitates the identification of genes in an experimental organism and their immediate location in man. There are two recent examples of this approach. First is the cloning of an obesity gene in the mouse and the identification of the human homolog the same day by computer search. Although no one knows the role of this locus in human obesity, there is now a specific candidate gene for etiology and pathophysiology studies. Second is the recent request for applications for studies to develop the genetic map in the rat issued because the investigators in hypertension are very close to mapping a number of loci that have significant effects in the different forms of the disease. The hope again is to move directly from the rat results to test for the importance of the homologous regions in the human genome.

6. Unresolved Issues. There are several additional areas of possible future research that have been identified in the discussions of directions for genetic studies: (a) The role of immune factors in the autism spectrum disorders is not resolved and warrants sufficient studies to clarify the situation. There may be indications that serotonin level and the immune response are correlated and this should be confirmed or denied as soon as possible. (b) MZ (identical) twins provide a unique experiment since they must share all their genes but are well documented to differ in important environmental factors including prenatal and developmental stochastic processes. The comparison of twins either discordant (one with autism, one

without) or concordant (both with autism) could provide insight into both genetic and environmental factors of importance. An issue for discussion is whether or not it is cost-effective and scientifically useful to mount a large epidemiologic twin study to identify a sample of MZ and DZ twins for study. There are very few twin pairs in the literature, most from European studies and single case reports (U.S.). Should the study be done in the United States or is an international study needed? (c) Numerous cases of autism are reported with chromosomal variants (trisomy, translocations, etc.) but many of these were identified before the high resolution banding studies were available and before breakpoints could be cloned and uniquely identified. These cases should be collected and the newer studies performed to assess whether or not there are specific chromosome changes involved with the clinical features of this disorder. (d) Linkage disequilibrium is utilized via haplotype sharing and association studies to more precisely pinpoint the location of genes than is possible through linkage studies. To successfully apply this approach it is necessary to utilize populations that are genetic isolates or those known to have descended from a few founders (i.e., Finland). Are there identifiable populations that fit these requirements in which autism spectrum disorders are documented to occur, and where the prevalence of the disorders would warrant initiating such studies?

BRAIN MECHANISMS

M. Denckla

Responses to NIH Questions

Question 1: What brain regions and functional pathways appear to be affected in autism? What key steps in development (timing, type, and loci) that are particularly sensitive to genetic or environmental insults are likely to be associated with autism? Research studies in autism in the last 15 years using a wide range of technologies have provided evidence of a biological basis for autism. Information from neuropathology indicates that there may be abnormalities in the amygdala, hippocampus, septum, mamillary bodies, and the cerebellum. Autistic brains are slightly larger and heavier. (Clinical measures also indicate a larger than normal head circumference.) In the limbic system, there is an excess of cells and they are too small. The neurons themselves seem developmentally immature with a truncation in the development of their dendritic trees, which provide the basis for connections between neurons. Moreover, Purkinje cells are affected in a widespread fashion in the cerebellum. The anatomic differences found are

consistent with a developmental curtailment that takes place at some point earlier than 30 weeks gestation (before birth). The neuropathologic findings are reasonably consistent and appear to dovetail with the lesion studies in primates. Exactly which findings are universal in autism and specific *only* to autism remain to be demonstrated.

Contemporary imaging research coupled with sophisticated neuropsychologic tools also offers exciting research possibilities for studying brain structure and function in vivo, particularly as new technology in both image acquisition and image analysis is developed. As with all research in autism, standardized diagnosis and control for age, gender, degree of mental retardation, language, and comorbid conditions are essential in interpreting these findings. The identification of reliably occurring subtypes and subgroups will be absolutely critical with all methodologies, as we can expect that a variety of brain structures and mechanisms may exist for subtypes with differing etiologies.

Across methodologies, studies reveal both higher and lower order areas that are dysfunctional. Neuropsychological studies have been uniform in finding deficits in certain aspects of higher order cognitive functions, including abstract and pragmatic language, encoding of complex information, and executive (frontal) functions. Other aspects of higher order cognitive functions, particularly those involved in verbal syntax and visuospatial organization are often spared in higher functioning individuals. Deficits in certain aspects of attentional functioning also are common and lower functioning persons with autism may also exhibit severe receptive and expressive language impairments, including mutism and a deficit in declarative memory. In contrast, rote memory often is intact. Evoked potential studies have also provided evidence of abnormalities in late information processing related to both frontal and parietal cortex. In contrast, evoked potential studies of early and midlatency potentials have demonstrated intact function in some subcortical areas. This neurophysiologic profile has been replicated with ocular motor, oculovestibular, and postural physiology methodology.

However, in terms of the timing, type, and locus of the originating abnormality in autism, the data from neuropathology suggest that other areas remote from the neocortex may be the beginning of the pathophysiological cascade. The universal impairment in social cognition found in neuropsychologic studies of autism suggests involvement of certain brain regions known to mediate social and emotional behavior, namely, regions of the limbic system, such as the amygdala and orbital frontal cortex. Animal research indicates that limbic lesions my cause secondary dysfunction in the neocortex. There is precedence in other diseases for this pathway, for example, progressive supernuclear palsy (PSP). Autopsy results in PSP show defects in the upper brain stem. However, PET scans in vivo show

frontal area dysfunction. Frontal area functions are closer to the surface and have an amplified effect on scans. The upper brain stem may not properly activate the frontal area. What is most obvious in in vivo imaging may not necessarily reflect the basic defect.

Taken together, the available evidence in autism suggests that, although certain aspects of brain functioning are often spared in autism, the syndrome nevertheless involves widespread brain dysfunction at both the cortical and subcortical levels. The originating site of the brain injury has not been identified. The competition of "top down" and "bottom up" hypotheses for the pathophysiological cascade in autistic development provides a fruitful area for future research.

At the subcellular level, neurochemistry research has provided consistent evidence of an elevation in a major neurotransmitter, serotonin, which affects potentiation at synapses and may play a role in the development of the nervous system. In terms of pathophysiology, it appears that there is a shared expression of a mutant gene in brain and platelet with respect to hyperserotonemia. Genetic analysis of the primary structure of the relevant neurochemicals is likely to be important for autism which has a sibling recurrence rate 4 to 10 times higher than that of insulin-dependent diabetes mellitus (IDDM) which has been found to have a genetic basis. Identified mutations could provide the first useful animal models of autism by homology, although animals will have a more limited behavioral repertoire.

Question 2: What behaviors observed in autism are consistent with the neuroanatomic findings? Neuropsychological animal and human studies have demonstrated the key roles that some of the brain areas affected in autism may play, particularly in social/emotional development. Studies of the amygdala indicate its importance in recognition of the affective (emotional) significance of stimuli, in social stimulus–reward associations that allow understanding of the connections between behaviors and their consequences, in perception of body movements and eye gaze direction, in orienting toward social stimuli, and, together with the hippocampus, its role in long-term memory. Representation of action plans, motor planning and execution, and working memory are associated with the frontal lobe and the basal ganglia. There have been reports of late-onset symptoms in the frontostriatal system in monkeys who experienced early limbic system lesions. Rapid shifts in attention and modulation of sensory input have been associated with the cerebellum. Neurochemical strategies could be used to study specific behaviors in response to specific neurochemicals that are most likely to have an impact on the development of those regions thought to be involved in autism.

In terms of etiology, much debate has occurred regarding the identification of a single primary deficit at the cognitive level. Rather than fo-

cusing on the identification of a primary brain structure that is abnormal, it is important to recognize that multiple structures at multiple levels of the neuroaxis have clearly been implicated and all these structures participate in the neural systems that influence behavior. The pathophysiology of autism, or the structural and functional abnormalities of the brain and how precisely they result in the abnormal behavior of autism is far more complex than what brain structures or neurochemicals are involved. Each level of analysis is highly complex and, at present, only pieces of this puzzle in autism have been identified.

Question 3: What are the critical influences that the process of development brings to the design of experiments and the interpretation of findings? Development clearly changes the outward expression of the signs and symptoms of autism. In addition, the changing signs and symptoms of autism must be compared to the changing backdrop of normal development in which the outward expression of normal abilities are also changing. In addition to variability associated with aging is the variability that occurs in normal humans in relation to general intellect and, in some cases, also gender and, in autism, in relation to severity of the disorder and developmental timing of onset, that is, congenital (at birth) or regression after apparently normal development. In assessing clinical functions, this means that different tests will be needed for different age- and ability-level individuals and that comparison groups must be matched on these relevant variables. With neurobiologic measures, these same variables of age, level of function, gender, and onset have a major impact and must be carefully considered in defining normative values and deviations from the norm. Several such methods including imaging and electrophysiologic cohesion measures have demonstrated that there are important and predictable changes in the relationships between measurements in different regions over the course of normal development. These factors require as careful attention to the selection of control subjects as to the rigor of diagnosis of autism.

Primate models also illustrate the importance of the role of development in the pathophysiologic cascade. Depending on the exact timing of the lesion, early injury to one part of the brain may result in later deficits in that part or in another part of the brain remote from the site of the original lesion. With certain known animal brain lesions, there is not much difficulty as an infant but there is significant social and working memory difficulty in adulthood. How profound the autistic-like behaviors are in monkeys depends on how early in the developmental process the brain lesions were made. Only through longitudinal animal studies can one find out what was primary and what was secondary. Longitudinal as opposed to cross-sectional studies could indicate whether subcortical findings are earlier and cortical findings are secondary to those deficits or vice versa.

Question 4: Does the available evidence suggest that there are prenatal/perinatal events associated with autism? If so, are they specific to autism, are they likely to be causal, and can they be used for clinical prognosis and the development of treatment strategies? The available evidence suggests that there may be more problems in pregnancy or at birth, or more health problems immediately after birth in children with autism than in control families. Risk factors such as maternal age, prematurity, bleeding in pregnancy, toxemia, viral infection or exposure, and poor vigor in the neonatal period have been studied. However, there is little evidence that these problems are consistent across cases of autism or that they are specific to autism since they are also found in disorders such as dyslexia or developmental language disabilities. Such problems do not predict to later autism, nor do they appear to be related to asphyxia. These factors do not appear to cause autism, but may be reflections that fetal or neonatal development was compromised in some way.

Recommendations of the Working Group on Brain Mechanisms

1. Investigation of brain structures in vivo with imaging methods is a major priority. At present, there are few data on most brain structures in autism. Cross-sectional, whole-brain studies at various ages are an essential first step in defining the relevant neuroanatomic focus for later studies. Functional MRI is a developing method that provides an opportunity for looking at the function of neural circuits without the hazards of radiation inherent to PET scans. Longitudinal studies in this area may be premature at this time until the rapidly changing technology stabilizes to allow for consistent measurements across time.

2. The use of the technology of neuropsychology, both human and primate, can help sort out specific aspects of clinical functioning and refine knowledge of hypothesized relationships between cognitive deficits and behavioral difficulties. Methodological developments in this research area are also needed to define the testing paradigms necessary for nuclear magnetic resonance imaging of the functional variety.

3. To expand knowledge of neuroanatomical findings, the need for access to a user-friendly brain bank was emphasized. Use of such a brain bank would lead to a greater number of appropriately age-, gender-, and cognitive-level matched controls being made available for study. Appropriate allocation of brain material to many different disciplines would allow the fuller use of postmortem brain samples for the study of specific anatomy and contribute to the urgently needed refinement of quantitative research methods for analysis. It would also permit staining of circuits that

are associated with certain neurotransmitter pathways for use in genetically driven studies about the action of protein.

4. Studies of primary structure of relevant neurochemicals by genetic analysis are needed, since genetic study is mainly a tool to study neurochemicals in terms of determining which, when, and where proteins are expressed in the developing nervous system. For example, proteins involved in the development of neurons shown to be abnormal from postmortem studies can be examined by DNA analysis available from blood or saliva from well-characterized patients who may be followed prospectively.

5. In an effort to identify key mechanisms in the pathogenesis of autism, studies of nerve growth and nerve growth migratory substances important for the modeling and remodeling of basic architectonics of certain centers of the human brain particularly important for language and social skills could be carried out. For example, family histories of affective disorder have been found in autism. In affective disorder, abnormalities have been identified in cell structure immediately adjacent to the inner surface of the cell membrane. This is also the site of action of neuronal growth factors, such as Growth Associated Protein, which guide the growth of developing neurons. This suggests an overlap or shared abnormal factor at the neurobiologic level in the regulation of brain membrane development in autism and affective disorder, particularly with regard to the inner membrane associated cytoskeleton. The association between autism and tuberous sclerosis may also be a particularly fruitful one in understanding the pathogenesis of both disorders. Research is also urgently needed that distinguishes two different developmental trajectories in autism, the one congenital (from birth) and the other characterized by apparently normal development followed by regression and onset of autism.

6. Two important considerations for future research include the need for developmental norms for many new methodologies and consideration of norms in relation to IQ, gender, and race. Much of what is known about brain function and neuropathology is based on acquired brain damage in adults. If neurobiologic strategies are to be effective in correcting structural abnormalities of the brain, then noninvasive technology for the study of higher order cognitive abilities and their neural substrate should be employed over the course of development. The majority opinion was that newer functional magnetic resonance imaging will displace PET scans for activation studies, particularly once the enlarged windows of brain visualization are perfected.

With regard to special considerations for such research, it is particularly important that normative data across the age span be accumulated with these new and more sophisticated methodologies for studying the brain such as volumetric MRI morphometry, functional imaging, and MR

spectroscopy. It is also important to define normal in consideration of subject variables likely to have a major impact on neuronal organization including age, IQ (particularly Verbal IQ), gender, and race (especially in studies of infants and toddlers where the acquisition of milestones varies by race). It is also important that controls be chosen and matched as carefully as the autistic subjects and that they too be thoroughly assessed for evidence of current and past history of neurologic and psychiatric disorders as well as for family history status. Use of structured instruments for these purposes should be routine.

7. Reports of abnormalities in higher order motor abilities (praxis) and higher cortical sensory abilities are now emerging. These findings may provide a basis for some of the unexplained aspects of the clinical syndrome of autism such as the sensory distortions (e.g., the relative insensitivity to pain and the sensory sensitivities) and movement disorders. Apraxis could provide a neurologic explanation for the inability of very young autistic children to use sign language. Sensory and motor abnormalities may be quite disabling and intervention depends on a better understanding of the neurologic basis of these behavioral difficulties. There is a related need for research on movement and synchrony, building on some previous research in this area and on new findings in Parkinson's disease and autism.

8. Replicable findings and consistency across methodologies will only occur when well-standardized methods are used for diagnosis, choice of comparison groups that control for relevant demographic and developmental variables, standardized protocols for imaging and psychological testing, and well-quantified methods of analysis. Such standardization is needed for all levels of inquiry neuro/pathophysiologic/anatomic, and etiologic (genetic and environmental), but progress at one level will not automatically result in solving questions at another.

COMMUNICATION/SOCIAL/EMOTIONAL DEVELOPMENT

M. Sigman

Response to NIH Questions

Question 1: What aspects of communicative, social, and/or emotional function/dysfunction are specific and perhaps universal to autism spectrum disorders (core deficits)? There is strong evidence that the capacity to share attention and emotion with others is specifically and universally impaired in autism. This is manifested in less joint attention and social referencing

in young children with autism, less understanding of the feelings and thoughts of others in older children with autism, and less initiation of social behaviors and responsiveness to others' feelings at all ages. Simple recognition of facial expressions is intact in many individuals with autism. However, understanding that requires the person with autism to take the perspective of another is generally limited. This deficit is also manifested in serious difficulties in the functional use (pragmatics) of language by those individuals who acquire language skills. Understanding and assessment of these deficits raise particular problems in research with nonverbal children.

Question 2: What is known regarding the developmental trajectories of these communicative and social behaviors in persons with autism spectrum disorders? Only a few longitudinal studies of children with autism have been conducted. From cross-sectional studies, it is clear that some of the problems with joint attention and social referencing improve as children's cognitive abilities develop. However, the deficits are manifested in higher level social and language abilities. Longitudinal studies suggest that the capacity for joint attention is linked to language acquisition but the child's sociability predicts to gains in language skills. There is stability in individual differences in responsiveness to other's emotions and this is independent of level of intelligence. Additional longitudinal data are needed for most aspects of these children's verbal and nonverbal communication and socialization.

Question 3: What is known about the specific contributions of biological and environmental factors to these behaviors? Very little is known about how biological and environmental factors contribute to these deficits although emerging interventions in this area show promise of demonstrating environmental impact on outcome.

Question 4: By examining other neurodevelopmental disorders that have autistic-like behaviors (e.g., temporal lobe lesions in early childhood; certain seizure disorders that involve behaviors reminiscent of autism which disappear with treatment), what can be learned about the nature of autism and its core deficits? Most studies of children with autism compare their behaviors to those of heterogeneous groups of children with mental retardation or children with language disorders. These children do not share the social deficits of the children with autism. Some of the same methodologies have been used to compare children with seizure disorders and children with autism. In studies of samples with more serious seizure disorders, the children with seizures but not autism are equally impaired in all forms of nonverbal communication. Children with autism are the most impaired in joint attention and the least impaired in gestures used to regulate the behavior of others. The overlap of autism with seizure disorders, particularly seizure disorders that result in regression after normal development, is an important area

of research. In general, onset of autism after apparently normal early development is poorly understood and underresearched. The literature on frontal and temporal lobe lesions in both animals and humans is informative regarding the timing and type of lesions that affect social development. Preliminary data from animal studies also suggest the possibility of recovery from early brain injury with treatment. This research has implications for understanding plasticity and the efficacy of early interventions but is not yet directly applicable to autism.

Question 5: Are there new models, methodologies, and/or statistical/analytic techniques that show promise in answering these questions? These are proposed in the following section of Recommendations.

Recommendations of the Working Group on Communication/ Social/Emotional Development

Four types of studies are recommended by the working group to address the gaps identified above.

1. Longitudinal Studies Which Follow Children from Early Childhood to Middle Childhood and Then on to Adolescence. Studies that assess either identical communicative and social behaviors over time or different measurements of the same constructs are needed. It would be interesting to do these in tandem with measures of the child's relationships with family members as well as measures of neurological, sensory, and motor functioning. Groups of children should be followed who meet diagnostic criteria for autism as well as those who fit into the spectrum even if they do not meet all the diagnostic criteria. Outcome measures should be broadened to include social understanding, competence, and relationships assessed in a variety of ecologically appropriate situations such as home and school. Studies could be designed to address the following questions: (a) How persistent are early deficits? (b) What are the consequences of these deficits? (c) What are the mediators of variation in development? (d) What are the best predictors of which children will develop speech and of which children will lose speech and develop autism after apparently normal early language development (up to one third of children with autism)? (e) Is there secondary deprivation (i.e., because children are not biologically prepared to respond to and interact with their environment, their initial deficits are worsened because they do respond normally to the usual, growth-promoting experiences in their environments.)? How do different families, schools, and treatment facilities act to prevent the deprivation that results from the child's communicative and social deficits? Are there different outcomes in these cases? (f) Can communication/social subgroups be identified and how

stable are these subgroups? (g) How do relations between specific deficits and neurological and cognitive functioning change with age? These studies could be linked to family studies so that the severity and persistence of deficits could be assessed in light of the characteristics of the families.

2. Studies of Early Diagnosis. Measures of early social and communicative functions (like imitation, joint attention, and social orientation) could be administered either to children with suspected developmental difficulties by parents, pediatricians, or day-care workers or to the infant siblings of children with autism. These children could then be followed to age 3–4 to validate the diagnoses.

3. Training Studies. Focused experimental interventions aimed at targeting abilities identified as specifically deficient in children with autism or predictive of later language and social skills could be carried out. These focused training studies would be short-term, intensive efforts to alter the child's communicative and social skills in a particular domain. They would supplement existing intervention or educational programs in which both experimental and comparison subjects are enrolled. Baseline measures would be made of neurological, sensory, motor, and cognitive functions. Training studies should be instituted during three age periods: *Early childhood*—Focus of intervention would be communicative skills, imitation skills, and/or affiliative behaviors. A multichannel approach (more than one type of sensory input, e.g., visual and auditory) could be used. *Middle childhood (nonverbal children)*—Preliminary research is needed to specify target behaviors since so few studies have attempted to identify deficits in communicative and social abilities in this age period. *Middle childhood to adolescence (verbal children)*—Focus of intervention would be understanding of the knowledge, beliefs, and feeling of the self and others.

4. Many individuals with autism lack speech and have limitations in gestural communication and in the use of augmentative communication systems. These problems areas may be caused or complicated by specific sensory difficulties and/or general motor or more specific motor/speech impairment. There is almost no systematic research in this area.

5. Multidisciplinary/Multicenter Studies. In some cases, multidisciplinary or multicenter investigations would be most effective. For example, in longitudinal studies of nonverbal and verbal communication skills, such investigations might allow examination of both biological and psychological development. This would make the research far more meaningful since continuity and change could be examined not only in each domain but also in the relations across domains. Longer term, multidisciplinary/multicenter investigations would also be necessary for linking family studies to longitudinal follow-ups of the autistic proband. Multicenter investigations would also be necessary when large samples are needed or to permit studies of

specialized populations, for example, an early diagnosis study using a high-risk sample, such as the infant siblings of children with autism, because of the small samples at any site.

MEDICAL INTERVENTION

D. Cohen

Responses to NIH Questions

Question 1: What are the most important goals for future research on medical interventions? There are two overriding objectives for future research on medical interventions: (a) rigorous evaluation of the effectiveness of currently available medical approaches to treatment; (b) facilitation of the creation of newer approaches to treatment that utilize advances in neuroscience, genetics, immunology, and other associated fields.

Evaluation of Treatment. The development and testing of biological interventions is a complex process that requires collaboration among clinicians and basic biological and behavioral scientists, including pharmacologists, psychologists, statisticians, and other neuroscientists. This process of clinical research should be embedded within suitable institutional contexts in which clinical care and investigation can be integrated, and in which there can be state of the art pharmacological and behavioral assessments of individuals with autism, at different phases of development and longitudinally. The infrastructure for this program includes the following components: (a) well-trained investigators familiar with the phenomenology and natural history of autism and with sophisticated methods of psychopharmacological research; (b) centers in which individuals with autism can be engaged in long-term biological research protocols, including inpatient and outpatient facilities, laboratories for biological and behavioral assessment, nursing and other staff for monitoring overall response, concurrent treatments, and support to assure long-term engagement of families in the research; (c) development and refinement of methodologies for assessment and for monitoring changes in various domains of functioning (including clinical rating procedures, behavioral observational methods, studies of functioning in important contexts, and laboratory-based assessments of cognition, attention, and other domains).

New Interventions. Advances in genetics, neuroscience, pharmacology, and other areas will continue to suggest new approaches to intervention. It is important to have investigators who are familiar with emerging areas of knowledge that may be relevant to autism (e.g., to new agents that are under

development). Also, there should be increased emphasis on finding treatments that are specifically related to the core problems of autism. Currently, all medications used with individuals with autism were screened on test systems that are not specific for core symptoms of autism (e.g., screened in relation to antipsychotic and antidepressant potential). They have been used with children and with individuals with autism, in particular, as orphan indications. There is no current program aimed at developing and testing agents that may specifically relate to core areas of autistic disturbance—social and communicative impairments. The development of new approaches may be based on increasing understanding of the biological preconditions for social attachment, for example, the role of hormonal systems in modulating attachment, on important systems (e.g., dopaminergic, serotonergic, noradrenergic, and peptidergic systems and their interactions) that are implicated in specific classes of symptoms, and on genetic factors in behavioral development and disorder (as these are elucidated). In the future, the field of genetic pharmacology will play an increasingly important role. This field integrates molecular genetics and biological interventions that are specifically targeted at changing the expression of genes. With the localization of specific genes and characterization of gene products that may be related to autism, a new era of biological intervention will be opened.

Recommendations of the Working Group on Medical Intervention

The design of biological intervention studies is complicated by heterogeneity among individuals with autism, the importance of following the effect of treatments over long periods of time to determine changes in developmental course, the many different agents and procedures that are available for study, and questions of informed consent.

1. A task force is needed to study improved approaches to the evaluation of treatment to complement the standard, double-blind, placebo-controlled trials. In addition to efficacy, it is important to have studies that relate to clinical effectiveness for diverse groups of individuals with autism and over longer periods. New statistical methods for assessment of developmental course (e.g., individual growth curve analysis) may be helpful, and statisticians, methodologists, pharmacologists, parents, and clinicians need to be able to work together as teams to design suitable approaches.

2. The use of medication is rarely appropriate without other treatment approaches, including educational and behavioral interventions. This collaborative approach will provide maximum benefit for the patients and data normally collected in educational settings can prove useful in evaluating

medical interventions in "real life." Once efficacy of a single aspect of treatment (i.e., medical or behavioral) is demonstrated, drug by behavioral intervention interactions can be tested, but increases in sample sizes needed to test such effects tend to be exponential in numbers and cost.

3. Currently available assessment methodologies are perhaps more useful for baseline assessment than for monitoring change. New methods for assessment may be needed for "lower functioning" individuals and for carefully following the course of treatment response in various positive domains (learning, social, emotional, cognitive) as well as on target symptoms (e.g., aggression, activity level). Functioning in situations of daily living needs to be assessed as well as symptom severity. Short- and long-term side effects need to be monitored.

4. Response to treatment may help define new subtypes of individuals with autism and lead to further understanding of biological subtyping.

5. In the assessment of individuals with autism, epidemiological study of dietary history and current functioning is needed. Studies are needed of the unusual eating behavior of individuals with autism (e.g., limited diets, craving for or avoidance of certain foods, eating unusual substances) which has been shown in other disorders to lead to elevated levels of lead or reductions in important dietary components. Such study may also reveal possible undiagnosed symptoms related to diet (e.g., MSG or lactose intolerance) or reflect metabolic disorders.

6. Pharmacological interventions may require the use of more than one medication at a time. For example, the treatment of some nonautistic individuals with obsessive-compulsive disorder may sometimes be improved by the augmentation of a serotonin reuptake inhibitor with a neuroleptic (e.g., fluvoxamine + pimozide). Similar clinical needs are presented by some individuals with autism. Systematic research is needed to understand the biological and behavioral effects of multiple drug use.

7. A coordinated plan for supporting rigorous, sustained clinical research on biological interventions in autism is needed. This includes (a) facilitation of training programs and career development in the field of pediatric neuropsychopharmacology and associated fields of clinical research; (b) creation of centers for long-term engagement in the field of biological clinical research. This initiative might be undertaken as an expansion of the current NICHD networks on pediatric pharmacology. Centers involved in this work should have the capacity for rigorous behavioral and biological assessment, integration of biological and behavioral interventions, and long-term follow-up; (c) establishment of multicenter collaborations for evaluation of biological and behavioral interventions (in which studies can be implemented, monitored, and carefully assessed over longer periods of time, including short-term improvements as well as long-term effects on de-

velopmental course); (d) NIH should work with advocacy and professional organizations to increase the awareness of parents, professionals, and government about the importance of rigorous scientific research on biological interventions. This includes helping parents and advocates recognize the value of volunteering for studies (including placebo-controlled designs) that may delay the onset of treatment for certain individuals but will ultimately benefit the individual involved as well as the advancement of the field by promoting authentic scientific knowledge that can inform treatment.

SOCIAL AND BEHAVIORAL INTERVENTION

W. J. McIlvane

The term "behavioral" in this context is intended to distinguish the primary thrust of this research from that of biomedical studies. The term "behavioral" is not limited to research in the tradition of applied behavior analysis or behavior modification, but includes the study of human and animal behavior from a variety of theoretical and conceptual perspectives (e.g., developmental).

Response to NIH Questions

Question 1: What is known and what needs to be learned about the effectiveness of specific types of interventions for specific types of children with autism spectrum disorders? Although there is no cure, autism is treatable through educational interventions of various types. Early intervention may be particularly effective, presumably because of the plasticity of the neural systems at that time. When to initiate treatment, how intensive such treatment needs to be, and how long to continue it are important research questions to be addressed. It is also clear that persons of all ages and levels of ability can benefit from access to consistently available, proven treatment. It is also known, however, that treatment response is not uniform within the population. Although many children may be brought to the point of near-normal functioning, others are much less responsive to social/behavioral intervention programs.

Question 2: What important outcome variables have been well studied? What additional outcomes need to be considered? Treatment research has demonstrated the feasibility of fostering significant gains in language, social adjustment, preacademic and academic achievement, and other desirable outcomes. The focus of many studies has been on compliance and on spe-

cific academic or preacademic achievements. Promising research has also been done on the acquisition of functional abilities such as changes in spontaneous communication and adaptive, flexible behavior over time which are more meaningful than changes in measurements such as IQ. Assignment to regular classes as the criterion for successful outcome is often meaningless because it reflects local political and legal mandates more than individual child need or status. As in other domains of intervention research, studies are needed to determine the long-term effects of all interventions (particularly early intervention).

Question 3: What are the diagnostic, methodological, and statistical issues that must be addressed in future behavioral and social intervention research? Research thus far has demonstrated that intervention, and particularly early intervention, offers significant hope for lessening the effects of autism. Many questions remain unanswered, however. Research is needed that uses robust experimental designs to evaluate and *compare* various approaches to treatment. Methods are needed that (a) involve random assignment to different treatment conditions; (b) use standard intervention protocols that capture a wide range of skills and symptoms, under both laboratory and "real life" situations; (c) make use of outside evaluators who are not invested in the outcome of the research; (d) assure high compliance with the defined treatment protocols to be sure that the intervention as designed is actually and consistently implemented; and (e) use longitudinal designs that evaluate treatment effects, both during the treatment itself, and at set points after the intervention has been accomplished.

The social/behavioral working group felt the need to identify (and perhaps to develop) research methods that would increase the likelihood that families would agree to the participation of their children in research studies. Newer statistical approaches (e.g., individual growth curve analyses) were encouraged. In particular, the working group felt that it was essential to distill a set of outcome measures that would have broad appeal for evaluating treatment approaches. While there was recognition of the significant potential for controversy in this area, it was felt that the problem could be managed and a reasonable set of measures might emerge if a broad constituency was involved in the development effort.

Question 4: What are the aspects of social policy that facilitate or impede research in this area? Recent developments in social policy, particularly the movement towards inclusion of individuals with autism (as well as other disabilities) in community schools, recreation, employment, and other activities of daily life are very influential on the ability to accomplish high-quality intervention research. While the goals of the inclusion movement were acknowledged and supported, there was considerable agreement that intervention should respond first to the needs of the individual with autism

(and his/her family), tailoring the approach to make it possible for each individual to achieve his/her full potential.

Some concern was also expressed that social policy advancement was needed to streamline the process of obtaining human studies approval for intervention studies. Although the committee was clearly aware of and duly concerned about the need to protect individuals with autism and their families in accomplishing research studies, the growing requirements for sometimes numerous, largely redundant reviews by multiple human subject review boards were seen as a possible obstacle in accomplishing certain types of intervention studies.

Recommendations of the Working Group on Social/Behavioral Intervention

1. A high priority for future research is studies that relate characteristics of individuals (or group subtypes) to treatment outcomes. Outcomes depend upon the interaction of the characteristics of the individual with the characteristics of the treatment approach. What works for one child may be ineffective or even counterproductive for another. Both categorical and dimensional approaches were discussed and may prove appropriate for defining such characteristics.

2. Too little attention has been given to environments and to the interaction of affected persons with aspects of their environments that typically affect child outcome. Particularly needed are studies of parent–child and sibling–sibling interaction over time, and of the effects of physical environments, behavioral modeling, relationships, exposure to speech, and technology such as computers that could contribute to more or less successful outcomes.

3. Another priority is research that would define the critical features of effective intervention programs for persons at different ages. At the present time, data have been presented regarding effective intervention "packages." It is critical to determine what aspects of the particular program, including family variables, and what intensity and duration of intervention are needed for successful outcomes at various child/adult ages. Post hoc testing to generate hypotheses for future research for targeting interventions is needed as well as hypothesis-driven prospective studies.

4. Collaborative, multisite projects appear necessary to obtain an adequate sample of children and intervention programs to assess subject by treatment interaction (i.e., what works best for which children) and to determine if the treatment can be effective in other treatment sites and samples with different persons implementing them.

5. As principles of effective treatment are increasingly well defined, research is needed to ascertain how best to encourage transfer of that learning for individual children (generalization) from clinic to home, home to school, school to community.

6. It is clear that all persons with autism are not currently receiving services based on the most advanced knowledge available. Mechanisms should be devised to expedite rapid transfer of research into practice.

7. There was agreement that maximally effective intervention would have to be a multidisciplinary effort. Without diminishing the value of well-focused individual research initiatives, high priority was accorded to research projects that could demonstrate truly effective, productive interdisciplinary interactions. For example, although methods derived from applied behavior analysis were acknowledged as especially effective in treating autism, it was thought that incorporating perspectives from developmental psychology and neuropsychology, among other disciplines, might enhance the effectiveness and acceptability of treatment methodologies. The importance of so-called "state" variables (nutritional status, drug status, etc.) was also deemed critical, and research to document state–treatment variable interactions was recommended. Implicit in these recommendations is the need for an organizing framework that is broad enough to incorporate inputs from the many disciplines that can make a helpful contribution to solving the problems of autism spectrum disorders.

8. If early intervention does substantially alter growth trajectories, as it appears, follow-up research will be needed to confirm that intervention does in fact produce lasting beneficial changes that would not be achievable without that intervention. Studies should be designed to ensure that the gains are not an artifact of subject selection or maturation. Some studies may incorporate imaging or other techniques that demonstrate potential biological (i.e., evidence of neuroplasticity) as well as behavioral change, particularly as higher-speed imaging techniques become available.

BIOSTATISTICAL RECOMMENDATIONS

H. C. Kraemer

Little more can be learned either from cross-sectional or from retrospective research on many key issues in autism. Autism is a developmental disorder, with very early onset, and is chronic over the lifetime of the patient. There is a serious need to understand what are the stable *traits* of patients and to distinguish these from what are the *stages* of the disorder, and to distinguish both traits and stages from *states* and *random variation.*

To do this requires prospective, longitudinal studies. The problem is that such studies are costly in terms both of research time and research cost.

New statistical methodologies are currently emerging to make such studies more informative as well as most cost-effective. Individual growth models have been mentioned frequently in this report, for example. Such models acknowledge both the consistant individual differences (traits) within groups of persons with autism and those differences expressed in different trajectories (stages). Moreover, such approaches are much more tolerant of unequal follow-up times, or irregular scheduling of follow-up times, and are much more robust to the less than perfect reliability of many available and pertinent outcome measures.

To reduce both time and cost of such studies as well, accelerated lifetime sampling methods are available, where subjects are entered into study at different ages and followed for some period of time (say 5 years), in such a way that age span over which different subjects are followed overlap each other. One can, by such methods, accumulate a depiction of the general growth patterns over the first 20 years of life, for example, using only 5 years of follow-up per patient.

There are many other such strategies either currently known but seldom used, or under current development, or that could be developed that are particularly appropriate to the study of this disorder. Development and dissemination of such methodological strategies might be supported for researchers in the field.

It is known that some persons with autism are high- and some low-functioning; that some are mute and some vocal; that some respond to a certain treatment and some not. Dr. Grandin made the point most strongly that there is a great degree of heterogeneity among persons with autism that is not well understood, and sometimes not even acknowledged.

Identification of subtypes is important, that is, subgroups of those appropriately diagnosed with autism who may have different etiologies, different course, and/or different response to treatment. If such subtypes exist, they are currently being lumped into one group. The heterogeneity so introduced by "lumping" diminishes the power to detect any signals, whether they be the genetic basis of the disorder, risk factors for the disorder, discrimination between persons with autism and those with normally developed brain structure and function, or treatment efficacy/effectiveness. It is crucial to future research and development of knowledge that, if such subtypes really exist, they be identified. On the other hand, we do not *know* the boundaries of autism or any subtype of autism. For example, we can reliably distinguish autism, Rett syndrome, and childhood disintegrative disorders (CDD), but are these simply different expressions of the same disorder or of different disorders (again, different etiologies, course, or

treatment response)? It should be remembered that before the organism for syphilis was identified, it was thought that there were multiple different diseases depending on which organ system was primarily affected. To "split" when there is no valid reason to do so may also undermine a research study's results. The search for a biological marker(s) is critical here.

Comorbidities are yet another problematic source of heterogeneity among persons with autism. Some comorbidities are random—one might have a cold and corns at the same time, and they have nothing to do with each other. Some comorbidities may be different expressions of the same disorder, or one disorder might lead to another. In such cases, these are not necessarily separate disorders, but perhaps different manifestations of the same disorder, or different stages of a single disorder. Some comorbidities are indeed separate but related disorders, due to linked genes or related environmental effects, or with common risk factors, some causal, some not. When comorbidity exists, each disorder may or may not affect the success of treatment of the other.

Should we "lump" or should we "split"? Each is appropriate in different situations, and whichever is inappropriate will compromise research success in understanding autism. It is essential to gain a greater understanding of the heterogeneities among persons with autism, and a recognition of which sources of heterogeneity are clinically important and which are not, for these issues have major repercussions in terms of research design and research success.

Another recurrent theme has been that of fostering closer connections between research efforts and real life. Patients, parents of patients, as well as interest and support groups should be involved in clinical research studies, both for the traditional purposes of fund raising and help with patient recruitment, but also to help researchers formulate the questions most important to patients. Along this line: (a) We should increase emphasis on long-term effectiveness rather than short-term efficacy studies. (b) We should reconsider the appropriate choice of control group (When is a placebo group the appropriate choice?), which may not be the same in all studies. (c) We should include consideration of both financial and emotional cost to families as outcomes in clinical trials as well as quality of life measures.

With the difficulty of defining samples that control for relevant variables and the severity and impact of autism, there should be special emphasis on high quality research, for example, diagnosis, sampling, measurement, design, and power. Frequently, the argument is made in the opposite direction: Since the issues are so important, we should allow researchers more latitude in designing and executing their studies. It is important to realize that funding poorly designed research is not only a waste of time and money that might better have been invested elsewhere but the

results may actually mislead the research field and misinform the clinicians working with patients with autism.

Moreover, it may well be that new modes of research collaboration need to be forged. Multisite trials are certainly one such example. Collegial agreements between independent research centers studying autism that a finding at one site should immediately be followed by an attempt to replicate and confirm that finding at another site, is another example. Autism registries, brain banks, and gene banks have also been mentioned as possible resources to foster excellent and cost-effective research efforts.

GENERAL RECOMMENDATIONS REGARDING RESEARCH IN AUTISM

1. A conference similar to this one should be convened in 2 or 3 years to assess the efforts and progress made.
2. The four funding agencies are strongly encouraged to coordinate support for autism research to help promote large-scale projects that would be difficult to fund within a particular institute.
3. To ensure a fair review of clinical research on developmental topics, at least one study section focused on the value and special needs of clinical research is needed.
4. Although coordinated, multisite investigations are clearly needed when large samples or immediate replicability is required, support for hypothesis-driven smaller studies by individual investigators should also continue to be encouraged.
5. Ethical issues of informed consent, withholding treatment in placebo/control designs, random assignment to different treatments, and impact of intrusive research and clinical procedures on this vulnerable population merit serious discussion with scientists, parents, self-advocates, and legal advisers.

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