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The Role of the Neurobiologist in Redefining the Diagnosis of Autism

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Until recently, autism, along with the other developmental disabilities, was largely ignored by the medical and research community. At this early point in our understanding of the syndrome, neurobiologists and especially those who work with human brain tissue have a great deal to offer. A thorough understanding of the clinically defined syndrome is essential. Along with the other psychiatric diseases listed in the Diagnostic and Statistical Manual of Mental Disorders (DSM), autism is defined by gross behavioral macros that, in all probability, are only indirectly related to basic biological systems. The diagnostic schema is not etiologically based. The diagnostic triad of symptoms that defines autism—impaired communication, impaired social interaction, and restricted and repetitive interests and activities—has been found to be present in the general population with no clear demarcation between pathological severity and being a common trait. In addition, the three basic symptoms of autism appear not to associate highly, thus leaving undetermined the validity of studying autism in its currently defined triad of symptoms. It is proposed that a close working relationship between neurobiologists and clinicians is necessary in order to identify etiologically based diagnostic schemas that would complement, rather than replace, the clinical diagnosis.

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Autism is a severe and common developmentally based disorder with symptoms that can be described as dramatic. It is generally believed that an experienced clinician or educator can recognize classic cases at a glance and quickly suspect the diagnosis even in less severely affected persons (20). It might seem surprising, then, to those who are not clinically involved with autism to learn that the classification or the diagnosis of autism is actually quite challenging. To take this further, it has been proposed that the current definition of autism is actually inhibiting our scientific understanding of the disorder (18). Human tissue research, as well as other neurobiological and developmental biology research, could make a profound contribution to advancing our understanding of autism. However, it is imperative that investigators have a sophisticated understanding of the clinical syndrome that is being studied. All too often biologists take the diagnosis for granted and devote all of their efforts to creating biological correlates to that diagnosis. I suggest that autism research will progress only if (i) it is understood that "autism" is a descriptor that likely comprises several etiologically based diseases, (ii) the individual dimensions of autism are studied separately as well as in combination with each other, (iii) there is a redefinition of autism based on developmental neurobiology instead of the current definition based on behavioral end points or "macros"; and (iv) human tissue researchers as well as other basic biologists are engaged in these undertakings.

PSYCHIATRIC DIAGNOSIS: A HISTORICAL PERSPECTIVE

In order to understand the diagnosis of autism, one must understand the psychiatric diagnostic criteria and how they were derived. Autism, like all mental disorders (as defined by the DSM), are phenomenologically based diagnoses (13). That is to say, we define autism based on observable and reproducible behavioral phenomena. The problem with this (which autism shares with the other psychiatric illnesses) is that the described behaviors are generally the "end points" of extremely complex biological systems. Historically, the field of psychiatry began with empirically based diagnoses (1). However, psychoanalysis, in addition to empiric observation, also relied heavily on speculations and hypotheses of the underlying mechanisms that caused mental illness. The popularity of these hypotheses, and their integration into mainstream psychiatry, too often led to false conclusions regarding the etiologies of various psychiatric diseases.

During World War II, a movement was started to systematize the diagnostic schema in psychiatry. This resulted in the DSM, first published in 1952 with a second revision (DSM II) published in 1968. Although the concept behind the DSM was to create valid and reproducible diagnostic criteria, in fact, these first two attempts were not successful. They were relatively simple and designed by a small group of clinicians who basically drew on their own clinical experiences which undoubtedly were influenced by the prevailing psychoanalytic theories of the time. In 1972, the DSM III taskforce was appointed to attempt the very bold step of defining diagnoses as objectively as possible (1). Psychoanalytic hypotheses were derived from single case studies. Causality was often assumed to occur from "unconscious" thoughts that could lead to the symptoms. Diagnoses such as homosexual panic (8) were explained by stating that the individual unconsciously feared his or her homosexual impulses, causing a breakdown in their defense mechanisms and leading to psychiatric symptoms. Schizophrenia was caused by the "double bind" placed upon the child by his or her mother

(2). In an especially tragic way, autism was thought to be caused by the "refrigerator mother"—a mother who lacked the empathetic skills needed for nurturing—thereby resulting in the child's extreme inward focus and producing the symptoms of autism (4).

It may seem remarkable to the 21st century reader that such theories were accepted etiological hypotheses as late as the 1970s but these were still being taught in psychiatric residency programs. Diagnosis during that time was more of an art than a science. In practice, psychiatrists would make diagnoses based on their own fondness for the theories rather than any objective criteria. Large studies proved that even the most severe psychiatric diagnoses were not being diagnosed with any acceptable reliability (26).

It was against this backdrop that the field of psychiatry made a very difficult and brave decision resulting in the DSM III. That decision was to recognize that the etiologies of psychiatric illnesses were just not known. The authors of the DSM then switched to the phenomenologically based diagnosis system that we have today. Given the need for a more scientific and reliable system of diagnosis, a large sacrifice was made. This was to accept diagnosis—possibly devoid of any etiological basis—in order to achieve reliability. However, it is this very compromise that may be hindering our understanding of autism today.

Autism was first included in the DSM III and was consistent with Kanner's description with some modifications. The main point to consider is the fact that the DSM diagnosis was validated against "clinicians' best judgment", and this remains to this day the method of describing and validating the phenotype (29, 30). Along with the diagnostic criteria, very elegant diagnostic assessment tools have been developed, most notably the Autism Diagnostic Interview-Revised (ADI-R) and the Autism Diagnostic Observation Schedule-Generic (ADOS-G). These instruments, which are based on the DSM diagnostic criteria, are often described as the "gold standard" and have become a necessary component of research quality diagnostic evaluations. Their administration requires training and reliability checks and takes a great deal of time. From a clinical viewpoint, these tools have been very valuable (29).

THE VALIDITY OF AUTISM AS A CONCEPT

The meaning of autism has been further explored by Happe et al (11). They question the validity of Kanner's original triad of symptoms as a unifying syndrome. They point out that research on autism has proceeded for half a century based on the assumption that the three impairments that define autism must be explained collectively despite little evidence regarding their integration. They contend that the impairments found in autism should be studied separately. Therefore, current research on the disease autism, as currently defined, is limited in that it will only involve subjects who have the three symptoms together.

Population-based studies can, however, clarify the situation, although until now this methodology has been rarely used. Recent population-based studies find that the symptoms of autism are found in the general population and the distribution of these traits forms a smooth continuum between those who have the diagnosis and those who do not (11). Further, no evidence of a bimodal distribution separating clinical from non-clinical levels of symptom severity has been found (7). In population-based twin studies using data from over 3000 twin pairs aged 7–9, only modest to low correlations of the behavioral traits were found. Correlations of 0.2–0.4 were found between communication impairment and both social impairment and rigid/repetitive behavior. Between social impairment and rigid/repetitive behavior the correlation was only 0.1–0.3. These findings were both in the general population and when the symptoms were more severe. Although the three areas of autistic-like behavior did occur in combination at above chance rates, in the vast majority of cases they did not and the three should be considered separately from each other (11).

The results of genome scans also contribute to this reconsideration. Although there have been many genetic studies, there has been little replicated linkage found, suggesting that searching for genes in "autism as a whole" should be abandoned. Autism is considered the most heritable of all the complex brain disorders based largely on the concordance rates in identical versus fraternal twins (9). A recent twin study (23) shows that heritability also separates according to individual traits. This is consistent with long-standing findings of studies looking at the families of autistic probands. In those studies, there is an increase in subclinical manifestations of all or part of the autistic triad.

The above discussion suggests that autism is a diagnosis that is not etiologically based and is composed of a collection of different traits that sometimes correlate but more often do not. These traits are found continuously in the general population as well as in the clinical population. In addition, autism (or the autisms) is known to be a heterogeneous group of conditions (20). There are many known causes or etiologies for the set of behavioral symptoms that describe autism and several of these have been well documented (19, 28). It is generally believed that the symptoms of autism are a final common set of behavioral outcomes that appear to have multiple etiologies and multiple pathophysiologies.

It could be conceptualized that, given all children as a set, we have created a subset of children who broadly fit into an aberrant developmental pattern. This subset has limits drawn somewhat arbitrarily, albeit reliably. We have labeled that subset as "autism" and have been, at times, less than exacting in allowing the assumption that this is an etiological valid disease.

WOULD WE WANT AN ETIOLOGICAL DIAGNOSIS IF WE COULD HAVE ONE?

Of all of the developmental disorders, there has been no research success story as exciting as the effort to describe Rett's Syndrome. Yet, despite achieving a major foothold on the etiology of Rett's Syndrome, the diagnostic criteria and classification have yet to change. In considering the possibilities for reconceptualizing autism, it is instructive to consider the experience of those who investigate Rett's Syndrome.

The autism spectrum disorders in DSM IV are known as the "pervasive developmental disorders" (PDDs) and include autistic disorder, pervasive developmental disorder—not otherwise specified, Asperger's disorder, childhood disintegrative disorder, and Rett's Syndrome (20). These are all described and classified based on observable behavioral symptoms. Since the publishing of the DSM IV, we have come to learn a lot more about Rett's Syndrome. Especially in young subjects, many of the girls meet criteria for autism (17);

yet we know that, etiologically, there are major differences. The MECP2 gene (16) accounts for up to 96% of classic Rett's Syndrome cases and is found rarely in autism. The initial genetic studies showed that 70%–75% of Rett's cases had MECP2 mutations. However, since then, the increased identification of mutations has changed that percentage. In addition, MECP2 mutations are found in atypical Rett's cases. MECP2 mutations have also been identified in a variety of clinical syndromes, including mild learning disabilities, neonatal encephalopathy, Angelman's disorder, X-linked mental retardation and autism. Clearly, knowing about the MECP2 gene, it would be foolhardy to continue to lump Rett's Syndrome with the other pervasive developmental disorders and expect to have a unifying etiology. Despite phenotypic overlap, there are diverging etiologies. It appears possible (and maybe likely) that in the next revision of the DSM, Rett's Syndrome will be separated from the other PDDs. This is not, however, a forgone conclusion. One might ponder the value of creating a diagnosis of MECP2 disease rather than continuing to use the behaviorally based diagnosis. From a neurobiological point of view, this would make a great deal of sense. Using the etiology of the disease as its defining characteristic will no doubt speed up the neurobiological knowledge of the disease and also may hasten the finding of treatments. In fact, Guy et al (10) report their ability to perform phenotypic reversal on a mouse model.

In 2001, an expert panel was convened to update the diagnostic criteria and they came to the conclusion that Rett's Syndrome is "a clinically and not a genetically defined condition" (14). The reason for this decision might lie in the broader issues of the multiple uses of, and advocates for, diagnostic nosology. From the point of view of the basic researcher, the closer one gets to the biological explanation the more valuable the diagnosis. Physicians in general might be better served by knowing the biological underpinning of the disease. In the case of educators (who are critical to current treatment interventions for children with autism), the situation is more complicated. One might argue that in establishing and directing schools for children with autism, the observable phenotype is more valuable than a hidden genetic polymorphism. Teachers probably will always be working with symptoms, and it makes more sense to have a classroom of children with similar problems than a classroom of special need students with dissimilar symptoms but a common genetic lesion. To look at this from another prospective, in autism—with a broader phenotype already present—it is possible that etiologically based subtypes might yield more efficient student groupings even in educational settings (27) although this is highly speculative.

Another important component of the autism community is the parent advocate and the legislators and administrators to whom they look for services. It is much more likely that family advocates will be successful in obtaining funding and services for an observable problem than for a hidden biological parameter. Miller et al (14) reviews the issue of genetic vs. clinical diagnosis for hemophilia and cystic fibrosis (along with Rett's), both of which, despite being genetically well described, continue to resist a genetic definition. Without the absolute one-to-one correlation of gene abnormality and observable clinical effect—which is rarely possible in medicine and that much more unlikely in the brain diseases—it appears that calls for a new genetically based taxonomy of disease (6), although intriguing, is unlikely in the near future. Others propose a multi-axial system to take into account the genetic and clinical factors as well as environmental factors (22). Yet again, the complexity of such a system appears daunting.

A BIOLOGICALLY BASED DESCRIPTION OF AUTISM

Despite the difficulties outlined above, a rigid adherence to a biologically flawed behaviorally based disease concept is not a viable option. Instead, one solution could be to develop appropriate diagnostic schema for each unique constituency. The community will have to be educated that, with biological advances along with the need of clinical relevancy, multiple diagnostic schemas may be needed for the same child. Epidemiologists, psychopharmacologists, educators, etc. might all benefit from a unique way of conceptualizing the problem. In reality, many autistic children already receive a medical diagnosis as well as a different educational diagnosis which is used for school programming. There is confusion; however, this could be overcome. For the neurobiologist, this diagnostic schema must reflect the neurobiological and developmental realities of autism.

The intensive study of autism is likely to yield many etiologies. Genetic models predict greater than 15 susceptibility genes (21). There is little doubt that environmental factors can also be a cause of autism, either alone or in combination with a genetic predisposition (18). Some recent exciting findings include associations with the genes EN2, MET, UBE3A, and several others (3, 5, 25). In these cases and in future findings, it is likely that the associations between genes and diagnosis will only be valid in a percentage of the autism cases. Finding these associations is very important and, clearly, these developmental genes are in need of further basic study to define the roles they play in brain development.

SCIENTISTS MUST TAKE THE NEXT STEP

A major rate-limiting step in making progress understanding diseases is the lack of translational research. This topic has been discussed widely and the National Institutes of Health and others have made, continue to make, attempts to encourage this type of research (31, 32). There are many descriptions in the literature of rodents with social difficulties and in many of these reports a statement is typically included suggesting that this is a model for autism. Very few investigators take that next step and demonstrate that the model is valid. Human tissue work provides one of the few links to study the role of genes in producing the disease study. A fuller understanding of the neurobiological underpinnings of some autism cases could point the way for valid subtypes not apparent through behavioral symptoms. It could be the case that if clinicians were able to subdivide populations based on biological parameters, clinically valid syndromes might emerge. For example, the very common finding of electophysiological abnormality and seizures in autism is still not well understood (12). A greater understanding of the origin of the electrical abnormalities might point to an etiologically distinct type of autism.

Another major, yet overlooked, issue relevant to the autism clinical phenotype is the understanding of which aspects of the phenotype are the result of genetic mutations (present from birth or *in utero*) and which are secondary to the lack of environmental stimulation (developing in the first years of life).

Rutter et al (24) examined 111 Romanian orphans who were adopted in the UK. These orphans were neglected in Romania. Six of them had autistic-like syndromes and another six had some autistic-like features. In the comparison group of adoptees born in the UK, no autistic symptoms were found in 52 children.

Although early childhood neglect has never been found in a significant number of autistic children, it could be that a baseline attentional problem caused them to be unavailable for stimulation, perhaps simulating neglect. A comparison between these orphans and more typical autism cases on a biological basis might yield important insights and might be discoverable by learning more of the effects of environmental stimulation or the lack thereof on brain development.

The involvement of biologists in the study of autism is relatively new. Until recently, the field was nearly all psychologists and clinically oriented physicians. The opportunities for neuroscientists in this field are great, as outlined by Moldin et al (15) in a paper entitled "Can autism speak to neuroscience?". Perhaps a better question would be "Can neuroscience speak to autism?".

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