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Diagnostically homeless and needing appropriate placement

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Guest Editorial

Diagnostically Homeless and Needing Appropriate Placement

THIS ISSUE OF JCAP focuses on children and adolescents with symptoms that suggest possible psychosis and/or disordered thinking. Their presentation arises from high-risk status because of strong family history of schizophrenia, developmental disorders where thought versus language communication is abnormal, and from atypical "psychotic" symptoms. In many ways, these young people are "diagnostically homeless" because they do not truly meet criteria for a *Diagnostic and Statistical Manual of Mental Disorders* (DSM) diagnosis, are given a "not otherwise specified" designation, and are never seriously studied in any systematic manner. The latter problem arises because they are either grouped with people who *do* meet criteria, or are excluded from study because they *do not* meet criteria for our nosological categories

This issue is a perfect one to dedicate to Barbara Fish, M.D., who is a pioneer child psychiatrist in the study of children at high risk for schizophrenia. She is one of the world leaders in the area of high-risk research in children and adolescents. We are honored to know her, to know her work, and to have her as a central contributor to this volume. Dr. Ted Shapiro, one of Dr. Fish's students, early collaborators, and a clinical investigator in his own right, has written a wonderful tribute to Dr. Fish, highlighting not only the importance of her work, but also the profound influence that she has had on numerous individuals in the field of child psychiatry, many of whom have become leaders in child psychiatric research. In fact, many of the contributors to this issue are Dr. Fish's professional first- or second-degree relatives (i.e., colleagues, mentees, and mentees of mentees).

Dr. Fish will be remembered for being one of the first people to demonstrate that early abnormalities of neurodevelopment were highly correlated with the development of schizophrenia spectrum manifestations. This is a finding that investigators continue to demonstrate (Carlson 2004). From a clinical standpoint, Dr. Fish's dedicated study of 23 people, from infancy through young adulthood, provides clinical insight into manifestations of serious psychopathology unlikely ever to be replicated. Detail is presented not only in terms of whether a symptom was present or absent, but how it actually appeared to the interviewer (Table 2 in the Fish and Kendler paper and Table 2 in the Carlson and Fish paper). Such detail is absent from more modern rating scales that tell you quantity and severity but not quality of symptoms.

The papers in this issue fall into three distinct categories: Those addressing schizophrenia spectrum disorders, those addressing studies of children at high risk to develop schizophrenia by virtue of their prodromal psychotic symptoms and/or family history, and papers which focus on children who have developmental disorders with multiple domains of dysfunction and comorbidities that can be confused with psychosis.

Schizophrenia spectrum conditions

Four papers address the question of the clinical aspects of schizophrenia spectrum symp-

toms in children. Three are from high-risk samples (Fish and Kendler, Carlson and Fish, Hans et al.), and one is a follow up study (Asarnow)

The first two papers in this issue consider the history of schizophrenia spectrum disorders from the inception of the concept of schizotypy by Paul Meehl in 1962 to the creation of criteria for schizotypal personality disorder for DSM-III. Interestingly, conceptualization of schizophrenia-like manifestations *in children* never appeared to be part of the thinking and developed its own line of research with, as usual, the child psychopathologists learning from research on adults, but, sad to say, no evidence of fertilization in the opposite direction.

An examination of the meticulously gathered, prospectively collected data on the cases reported in the papers by Dr. Fish, and Hans et al. reveal two important findings. Firstly, elementary school children with a variety of behavioral (e.g., aggression), developmental (wide-ranging skill deficits), and emotional (anxious, depressed appearing) symptoms can be distinguished from other children with such symptoms by their social isolation, apathy, mild thought disorder, and suspiciousness. These "negative" symptoms, more than psychosis, seem to set them apart. Secondly, long-term follow-up demonstrates the persistence of symptoms. In two cases (Andy from Carlson and Fish; David from Hans et al.), a mood disorder was superimposed on the backdrop of schizotypy but did not change the overall course. Confirmatory evidence comes from Asarnow's shorter-term follow-up study with data collected in more "modern" ways (e.g., semistructured interviews, specific criteria elicitation). Not only was schizotypy stable in half the cases, but even in this sample, where mood disorders were later manifested, schizotypal symptoms persisted (hence, schizoaffective and atypical bipolar designations).

Perhaps, then, rather than saying that "personality disorders have an onset in adolescence and early adulthood," thus leaving children diagnostically homeless, a clarification is necessary. This supports the belief that adults with certain "personality disorders" may not have personality disorders at all, but rather an Axis 1 spectrum condition that, like the Axis 2 disorder, can be evident at any age,

Implications of psychosis for the development of schizophrenia

The paper by Stone et al. is a theoretical paper which bridges the gap between the clinical phenomenology of schizotypy manifestations to the liability to schizophrenia (called "schizotaxia"). Rather than examining children, the paper reviews genetic high-risk studies and assesses them for features that may be related to schizotaxia or core features of genetic liability. A reading of the tables in this paper reveals the common denominators found in genetic high-risk studies (schizotaxia) and schizotypy. Not surprisingly, there is considerable overlap between the risk factors found in large, genetic high-risk studies (Stone et al.; Tables 3 and 4) and the clinical symptoms of schizotypy reported by Carlson and Fish (Tables 2 and 4). The authors conclude by saying that high-risk studies are important for a variety of reasons, including the ultimate identification and validation of specific liability syndromes.

There are two approaches to understanding liability to severe psychiatric disorder—in this case, psychosis and schizophrenia. Firstly, there are the genetic high-risk projects that research individuals at-risk for developing psychosis based upon having a first-degree relative with schizophrenia. Dr. Fish, and somewhat later Drs. Erlenmeyer Kimling and Cornblatt, and also Marcus and Hans, played major roles in this field of research. More recently, methodology has focused on ultra high-risk studies. These go beyond the genetic vulnerability and identify clinical features that are indicative of heightened vulnerability for the imminent onset of psychosis.

The challenge is to define the prodrome of psychosis. Prodrome is the period preceding the first episode of psychotic illness and consists of an emergence of nonspecific psychiatric difficulties that are subtle and pose significant diagnostic and treatment dilemmas. A central goal of ultra high-risk research is to develop a system for identifying patients during the prodrome of illness so that they can be monitored,

and so that treatment delays can be reduced. This issue includes four papers that examine children and adolescents with psychotic symptoms that do not meet criteria for schizophrenia or mood disorder with psychosis, and the goal is to determine the course of those symptoms, and the clinical entities in the youths manifesting them.

Meyer et al. provide an excellent review of the issues and concepts of prodrome as it has evolved in recent decades. As part of the University of California—Los Angeles (UCLA) Center for the Assessment and Prevention of Prodromal States, the authors systematically characterized 24 adolescent patients felt to be at imminent risk for psychosis. It was necessary to screen 139 subjects who were thought to be prodromal, in order to find these 24 who were symptomatic enough to be prodromal, but were not so symptomatic they were already psychotic. Necessary to characterize the subtle symptoms these youths manifest are a number of sensitive and lengthy interviews designed to elicit the cognitive and behavioral pathology not always evident in the usual structured interviews used in child psychiatry research. Attenuated positive symptoms were most prominent in this sample (perceptual abnormalities/hallucinations and unusual thought content), for which reason they were felt to be in the "late prodromal phase." Many already had significant social and attentional problems. Major depressive disorder was diagnosable in half the sample, but at least as important were wide-ranging subsyndromal conditions. The question is whether these patients will stabilize at this point and remain more schizotypal or continue into a full-blown psychosis.

Also using the ultra high-risk paradigm, Correll et al. describe their adolescent prodromal sample from the Zucker Hillside Hospital's Recognition and Prevention Program. The methodology, not surprisingly, is similar to that described in the UCLA project. However, Correll et al. chose to emphasize and review the implications of heterogeneity of psychotic symptoms that were either fewer in number than required for schizophrenia ("psychosis not otherwise specified (NOS)") and or lasting more than a day and less than a month ("brief psychosis"). Like other diagnostically homeless youths, those with either of these two diagnostic entities have been neglected in terms of systematic research and are variably included, if at all, in either the at-risk group or in the outcome group (schizophrenia).

In the study by Correll et al., 29 youths were characterized at baseline, and 26 were available for follow up (>6 months). These authors found that the diagnoses of psychosis NOS ($n = 22$) and brief psychotic disorder ($n = 4$) are unstable and heterogeneous entities. The psychosis in 3 of the teens with brief psychotic disorder had remitted as had the psychosis in 7 of those with psychosis NOS. On the other hand, 9 had progressed to further psychosis (5 schizophrenia, 3 bipolar with psychosis, 1 schizoaffective). The underlying, or additional Axis I disorder remained, for the most part.

Hlastala and McClellan characterize the phenomenology and diagnostic stability of youths in a long-term psychiatric hospital with atypical psychotic symptoms. In a 2-year follow-up study, they compared three groups of youths; those with atypical psychosis, those with schizophrenia, and those with bipolar disorder with psychotic features. They assessed general symptoms, comorbid diagnoses, prior abuse, and overall functioning. Like Correll et al., the authors found that those with atypical psychotic symptoms were very heterogeneous. None developed classic psychotic illness by the 2-year follow-up. These individuals with atypical fleeting or situationally specific hallucinations had higher rates of abuse, dissociative symptoms, and were more likely to have posttraumatic stress disorder or a depressive disorder than current or true prodromal psychotic illness. These authors conclude it is not even appropriate to designate some symptoms as truly psychotic.

Finally, Stayer et al. tackle the diagnostically homeless children from the National Institutes of Mental Health (NIMH) Early Onset Schizophrenia project for whom a new term, "multidimensionally impaired," had to be coined to classify the children. In this research designation, the psychotic symptoms were defined as "poor ability to distinguish fantasy from reality as evidence by ideas of reference and brief perceptual disturbances during stressful periods or

while falling asleep." These symptoms were superimposed on children who appeared to have affective dysregulation and attention-deficit/hyperactivity disorder (ADHD)-like symptoms. The thrust of this paper is that some of the children (5 of 32) were virtually asymptomatic, though the remainder were still significantly impaired (4 of the 10 had ongoing psychosis and all 10 continued to have severe behavioral disorders) albeit not schizophrenia.

Diagnostically homeless with possible pervasive developmental disorder

Children with developmental disorders tend to present to clinics with multiple domains of dysfunction, including the areas of mood regulation, attention, and thinking. These youths also have some features of pervasive developmental disorder and a number of non-DSM categories have been proposed over the years to more accurately capture these nosological orphans, including: Childhood-onset pervasive developmental disorder (PPD) (DSM-III; American Psychiatric Association, 1980), multiplex developmental disorder (Towbin et al. 1993; Cohen et al. 1987), multiple complex developmental disorder (MCDD; Buitelaar et al. 1998; Buitelaar et al. 1999; Van der Gaag et al. 1995), and multidimensionally impaired disorder (McKenna et al. 1994). These children are quite common within clinical settings, yet little is known about them longitudinally and in terms of treatment interventions. The reasons for the lack of knowledge and progress as it pertains to these youth is complicated, but it is clear that research in these children has been somewhat hampered by the fact that they do not fit into our nosological categories in a clear way.

The first issue that arises in examining children with atypical PDD symptoms is whether and how they differ from children with high-functioning autism. Van Der Gaag et al. provide an excellent summary of an often vexing distinction—that between a language disorder and a thought disorder. Then, using Caplan's Kiddie Formal Thought Disorder (FTD) Story Game and Rating Scale (Caplan et al. 1989) to systematically assess thought disorder, they examined children with clear high-functioning autism, those with "MCDD," children with two other psychiatric disorders (anxiety and attention-deficit/hyperactivity disorder), and normal children. The authors found that the autism and MCDD groups had similar rates of formal thought disorder and were clearly different from the other groups. Loose associations were almost specific for the PDD groups. While these findings suggest that MCDD is an autism spectrum condition, the authors also conclude that FTD in the autism and MCDD populations probably reflect pragmatic, discourse, and specific information-processing deficits rather than schizophrenic-like thought disorder. Misdiagnosis of such children as having schizophrenia, then, is quite easy, and one suspects that such young people have found their way into studies of schizophrenia. This is not a trivial problem, considering the different treatment implications for autism and schizophrenia.

Another question that arises when examining children who have some symptoms of pervasive developmental disorder is how much the constellation of symptoms that certainly appear to be on the autism spectrum should represent a legitimate comorbidity that needs its own designation (e.g., multiple complex developmental disorder, childhood-onset pervasive developmental disorder). Two papers discuss its comorbidity with other Axis I disorders. For instance, the study by Towbin et al. evaluated the presence of autism spectrum disorder symptoms (ASD) in youths in a mood and anxiety disorders program. They tried to exclude children with known autism or Aspergers' disorder but found, using the Social Communication Questionnaire, Children's Communication Checklist and Social Reciprocity Scale, that 62% of the 93 patients enrolled in the programs screened positive for a possible ASD on one of the instruments that the authors used. One case example illustrates obvious comorbid bipolar disorder with this autism spectrum condition.

It is instructive to note that the three instruments used in the Towbin et al. paper to measure some of the same constructs are hardly mutually inclusive. One (Social Communication Questionnaire) is basically an instrument developed to screen for autism, and is the most

conservative instrument. The Children's Communication Checklist really hones in on language disorders with some symptoms that pick up on autism. The Social Reciprocity Scale includes items that address autism, immaturity, schizotypy, and general peer relationships. Thus, each tells us something different about the sample of bipolar and mood-dysregulated children. Given the impact of language dysfunction and peer relationships on outcome, however, the absence of a way to classify this comorbidity means that we cannot usefully predict outcome, except as the tried and true "poor premorbid functioning" variable that broadly assesses the same issues.

Weisbrot et al. examine the frequency of anxiety symptoms in preschool and 6–12-year-old clinic children with and without pervasive developmental disorder symptoms. In this case, the authors use parent and teacher endorsements on the Early Childhood Inventory (Gadow and Sprafkin 1997) and the Child Symptom Inventory (Gadow and Sprafkin 2002) to classify the children. What makes these children especially complex diagnostically is the fact that they also have significant rates of psychotic symptoms, compared to nonanxious children. Anxiety and psychosis are well-accepted "comorbidities" in people without developmental disorder. Although the psychosis was related to the degree of anxiety, rather than PDD, one might speculate that a youngster who has social oddities, pragmatic language problems, and psychotic-like symptoms might well be mistaken for having a schizophrenia-related disorder. This is less likely to happen in a child without this developmental complication.

The volume ends with an interesting and complicated case of a teenage girl with an underlying mitochondrial disorder who has psychiatric symptoms. The case report discusses the neuropsychiatric manifestations that can be seen in these youths and highlights the sometimes atypical response of these individuals to psychotropics. In this case, the awareness of JM's doctors of this unique drug-induced response saved the patient from a psychosis diagnosis, and more importantly, from treatments that might have made her worse. The authors emphasize the need for systematic evaluation of treatments for emotional and behavioral symptomatology in youths with these disorders.

CONCLUSION

The reader may wonder why a JCAP issue addresses *no* psychopharmacology. It seems to us that the clinical implications of these purported psychotic symptoms in children and adolescents is wide ranging. Firstly, a diverse group of authors with different backgrounds and studies have ended up reporting on issues with considerable similarity. Also, mild negative symptoms are disabling, enduring, and can start early in life. They have clear neurodevelopmental origins. Secondly, not all psychotic symptoms are created equally. Some are transient, in fact, and appear to be superimposed, almost incidentally, on other Axis I conditions. Thirdly, some are phenocopies and, in the context of a pervasive developmental or autism spectrum disorder, can be misinterpreted as psychosis. Absent of a good way to classify children with these symptoms, measure them reliably, and study their treatment, these diagnostically homeless children are likely to be exposed to treatments they may not need and not given treatments they do need.

Instruments and interviews to further study this population of children will need to include developmental assessments for pervasive developmental disorder, prodromal symptoms, Axis I disorders, and cognitive and language functioning. Conspicuously absent from most of these otherwise excellent papers is any feeling for what the content of the hallucinations, delusions, and negative symptoms were. Although reliable ratings help us quantify the problems, they clearly have not helped us distinguish clinically the inconsequential from the serious problems nor do they help a clinician recognize and distinguish differences. Perhaps only other, nonpsychotic symptoms, or imaging or biological markers, will be able to do that. Family histories will need to include not only adult Axis I disorders but also possible childhood disorders that may have persisted in parents (e.g., partially remitted autism spectrum disorders, schizotypal personality disorder, learning and language disorders).

With better assessment and classification in place, we may be able to dedicate a future issue to formerly diagnostically homeless children who have not only found respite but also appropriate treatment.

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Dr. Barbara Fish (front row, center) at a lunch with colleagues, friends, and protégées from UCLA-Neuropsychiatric Institute, January, 2003. (Dr. Fish was recovering from a fractured hip). People pictured from left to right: Gabrielle A. Carlson, MD, Barbara Fish, MD, Margaret Stuber, MD, Joan Asarnow, PhD, Marian Sigman, PhD, Bonnie Zima, MD, Rochelle Caplan, MD