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EDITORIAL

Attention deficit hyperactivity disorder in adults[1]

Adults with putative attention deficit hyperactivity disorder (ADHD) are increasingly being referred to psychiatric clinics, often following a self-diagnosis, and demanding a prescription for stimulant medication. This has disconcerted many clinicians and started a debate on the appropriateness of this diagnosis in adults (Shaffer, 1994; Lomas, 1995; Diller, 1996) that is reminiscent of the controversies of the childhood diagnosis in previous years (*Lancet*, 1986). At issue is not only concern about the widespread use of stimulant medication, but also a neurobiological understanding of impulsivity, hyperactivity and antisocial behaviour and the genesis of some psychiatric disorders in adults. How is the validity of this disorder in adults then to be established?

First, it is useful to remind ourselves that diagnoses are concepts that evolve over time and their usefulness is judged by their ability to inform us about pathophysiology, treatment, possible prevention and prognosis. In psychiatry, most diagnoses continue to be based on symptomatology and course of illness, and their validity must be determined in the absence of gold standards. While construct and concurrent validity are important, predictive validity in terms of treatment and prognosis is pre-eminent in most diagnostic determinations (Kendell, 1989). Furthermore, the tension between categorical and dimensional approaches to classification has not eased completely, with clinicians generally finding the categorical approach more appealing. These principles apply to adult ADHD as much as to other psychiatric syndromes.

Secondly, a seemingly simple argument! If the diagnosis of ADHD in childhood can be unequivocally established, and longitudinal studies can demonstrate the continuation of the disorder into adulthood, the status of the adult disorder would not be difficult to validate. The alternatives are that either the disorder remits in adolescence in *all* cases, or the adult manifestations are categorically distinct from the childhood manifestations such that a different diagnostic label is appropriate.

Controversy exists in relation to its prevalence and its operational criteria, but childhood ADHD is firmly established as a diagnostic entity in child psychiatry clinics. In the United States, as many as 50% of clinic attendees are given the diagnosis of ADHD (Cantwell, 1996), and prevalence rates are estimated at 3–5% in the general population (American Psychiatric Association, 1994). The diagnosis is used much less frequently in the United Kingdom (Hoare, 1993) and Australia (Rey & Hutchins, 1993) and this appears to reflect differing diagnostic criteria being used. The ICD-10 (World Health Organization, 1992) has adopted a more restricted definition of the 'hyperkinetic syndrome' than DSM-IV. No classificatory system has, however, dismissed the diagnosis outright. When diagnostic criteria are used consistently, cross-national differences in prevalence seem to disappear, as evidenced by two recent epidemiological studies in children. A Tennessee, USA, study (Wolraich *et al.* 1996) reported prevalence for the primarily inattentive, primarily hyperactive, and combined subtypes of DSM-IV ADHD at 4·7%, 3·4% and 4·4% respectively. The corresponding figures from a German study (Baumgaertel *et al.* 1995) were 9·0%, 3·9% and 4·8% respectively. These figures are higher than those obtained using DSM-III-R criteria, further highlighting the impact of the chosen set of criteria on prevalence estimates.

Does this childhood disorder persist into adulthood? Several studies have prospectively followed up child ADHD subjects into adolescence but only two have continued this into adulthood (Weiss *et al.* 1985; Manuzza *et al.* 1993). The first (Weiss *et al.* 1985) followed 63 of an initial cohort of 104

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children to a mean age of 25 years (range 21–33) and reported that about half had continued to have mild to severe symptoms of the syndrome and were functionally impaired. This study did not use diagnostic criteria in adulthood. The more recent study by Manuzza and colleagues which examined 91 male subjects, comprising 88% of a cohort of hyperactive children, at a mean age of 25·5 years (range 23–30), was methodologically more rigorous. At follow-up, 8% (cf. 1% controls) had a DSM-III-R diagnosis of ADHD, suggesting a marked decline of ADHD symptoms from adolescence to adulthood. The prevalence of antisocial personality disorder and drug abuse disorders was high in the ADHD cohort. Hill & Schoener (1996) analysed nine prospective follow-up studies and documented an exponential decline of about 50% of ADHD rates over time. Estimating a prevalence of 4% in childhood, the predicted prevalence was 0·8% at 20 years and 0·05% at 40 years. The conclusions to be drawn are: (*a*) the childhood disorder does persist into adulthood when studied longitudinally, and (*b*) the prevalence of this disorder in adulthood is low in comparison with that in childhood. It is possible that the rates would be higher if ADHD children with co-morbid conduct and oppositional disorders were included in the follow-up. Prevalence data on adult ADHD obtained directly from community studies are not currently available, and this constitutes a major gap in the literature.

Studies that have examined the putative adult syndrome cross-sectionally have reported a symptom profile or factor structure similar to that of the childhood syndrome (Borland & Heckman, 1976; Morrison, 1980; Shekim, 1989; Biederman *et al.* 1990, 1993). Early data suggest that this profile is independent of the referral status of the subjects (Biederman *et al.* 1990) and consistent across genders (Biederman *et al.* 1994). The adult syndrome results in interpersonal, occupational and cognitive impairment that is similar to that in childhood, after accounting for age-appropriate expectations (Borland & Heckman, 1976; Biederman *et al.* 1993). The impairment increases incrementally from nil to partial to the full syndrome (Mannuza *et al.* 1993; Biederman *et al.* 1994). Cross-sectional study, therefore, yields an adult syndrome that is consistent with the childhood description of the disorder. The relative importance of inattention, hyperactivity or impulsivity in the diagnosis poses problems in adults more so than it does in children since the longitudinal course of these three features is not known. The DSM-IV practice of diagnosing one syndrome with emphasis either on inattention or hyperactivity/impulsivity, in contradistinction with two distinct syndromes (Lahey *et al.* 1984), remains controversial. Further research may help clarify the appropriateness of subtyping the syndrome and lead to a refinement of the criteria in adult diagnosis.

A fundamental issue of course is whether ADHD can have an onset in adulthood. The disorder is currently conceptualized as being neurodevelopmental with an onset childhood, and a primary adult-onset syndrome has not been proposed. While genetic factors are considered to be most important in the aetiology, a number of other causes are known to contribute to ADHD in a minority of cases: prematurity or low birth weight (Cantwell, 1996), prenatal and/or perinatal insults due to trauma, toxins (maternal smoking or alcohol abuse) and infections (Barkley, 1990), childhood exposure to toxins (e.g. lead) (Thomson *et al.* 1989), fragile X syndrome (Turk, 1992) and possibly generalized resistance to thyroid hormone (Hauser *et al.* 1993). These factors are thought to operate in childhood to either bring out a genetic vulnerability or produce phenocopies of the disorder. Diagnostic criteria for adult ADHD, owing to this conceptualization, require an onset in childhood which is not unlike other neurodevelopmental disorders such as Tourette's syndrome (TS). It is conceivable that brain insults during adulthood, e.g. brain trauma or infection, may produce a disturbance of attention or hyperactivity/impulsivity similar to that seen in ADHD. Current evidence does not clearly distinguish the core features of ADHD – inattention, hyperactivity and impulsivity – from similar features produced by other brain disorders. If the neurodevelopmental perspective is taken, a diagnosis of ADHD would not be justified if normal development of attention and impulse control had occurred prior to the brain insult. The approach is similar to TS in that tics due to other causes such as neuroleptic or anticonvulsant drugs, brain trauma, encephalitis, etc. are not diagnosed as TS. This does not mean that the study of disordered attention in adults is not worthwhile; such disturbance is most commonly secondary to other

clinical conditions and should not be given a diagnostic status of its own. Nevertheless, an examination of the qualitative differences between the attentional difficulties in ADHD and those in other disorders such as depression, schizophrenia, etc. would be of considerable interest.

A challenge to diagnosticians of adult ADHD is the confirmation of the age of onset. The reliability of retrospective reports of childhood behavioural abnormalities has been challenged (Yarrow *et al*. 1963; Manuzza *et al*. 1993), although Biederman and colleagues (1993) suggested that what was necessary was systematic enquiry. Wender *et al*. (1981) noted that parental recall, if available, was more reliable than that of the patients' themselves. School reports may provide objective evidence of age-inappropriate behaviour except that such reports are difficult to obtain.

The diagnosis of adult ADHD is confounded by co-morbid disorders and other psychiatric disorders that share its symptoms. Adults with ADHD are particularly likely to suffer from cluster B personality disorders and substance use disorders, and have an over-representation of mood, anxiety and somatoform disorders in some studies (Tzelepis *et al*. 1995), making the diagnostic attribution of a particular symptom ambiguous. One widely used set of diagnostic criteria of adult ADHD, the Utah criteria (Wender *et al*. 1981), which also needs a childhood onset, does not permit the diagnosis of adult ADHD if bipolar disorder, major depression, schizophrenia or borderline personality disorder is diagnosed. Yet, it has been possible to demonstrate that the core features of ADHD remain when the symptoms of the co-morbid diagnoses have been subtracted (Biederman *et al*. 1993). Furthermore, longitudinal studies support the occurrence of a pure syndrome of adult ADHD with little or no co-morbidity in a small proportion (Manuzza *et al*. 1993). The issue of co-morbidity raises some important questions for research in relation to adult ADHD: (*i*) Does ADHD in childhood predispose to the development of personality disorders in adulthood?; (*ii*) Is a co-morbid conduct disorder a predictor of the later development of antisocial personality disorder?; (*iii*) Are children with ADHD at an increased risk of bipolar affective disorder or cyclothymic disorder, and does ADHD persist when this occurs?; and (*iv*) Should there be a separate subtype of ADHD designated as 'aggressive type'? It is important that longitudinal studies of ADHD into adulthood address these issues, and treat co-morbidity as an important determining variables rather than 'noise' (Jensen *et al*. 1997).

Attempts to validate ADHD, both in children and adults, have received considerable impetus from genetic and neuroimaging studies, but many questions remain. The evidence for the role of genetic factors from research in children and adolescents is compelling but the precise mechanisms involved and proportional contributions made are uncertain. Family studies have all reported familial aggregation of ADHD, with the suggestion of autosomal dominant inheritance (Deutsch *et al*. 1990; Faraone *et al*. 1992). Findings of increased prevalence of other psychiatric disorders in the relatives of ADHD probands have been inconsistent (Borland & Heckman, 1976; Lahey *et al*. 1988; Biederman *et al*. 1992). Adoption (Morrison & Stewart, 1973; Deutsch & Swanson, 1985) and twin studies (Willerman, 1973; Goodman & Stevenson, 1989; Levy *et al*. 1997; Sherman *et al*. 1997), although limited in their methodology, have pointed in the direction of a substantially greater genetic than environmental role. Twin data (Sherman *et al*. 1997) suggest that the dimensions of inattention and impulsivity-hyperactivity are both heritable and mediated by a common genetic factor. The high concordance in monozygotic twins suggests high penetrance of a putative gene. Some genes implicated to date are: HLA on chromosome 6 (Cardon *et al*. 1994), dopamine transporter gene on chromosome 5 (Cook *et al*. 1995), and D4 dopamine receptor gene on chromosome 11 (LaHoste *et al*. 1996). It is likely that multiple genes may be implicated, even in the same individual (Levy *et al*. 1997). An important limitation of the genetic research is that heritability estimates differ greatly depending upon the informant source relied upon (Sherman *et al*. 1997). Statistical methods are generally used to deal with informant bias, but there is a real need to determine the basis for such differences across informants (Rutter, 1997). ADHD has a well-documented association with Tourette's syndrome, a disorder with a well-established genetic basis (Coming & Comings, 1988) and, interestingly, with a rare syndrome of generalized resistance to thyroid hormone, an autosomal dominant disorder linked to the human thyroid receptor-β gene on chromosome 3 (Hauser *et al*. 1993).

The genetic studies have not settled the debate whether ADHD is best conceptualized as a categorical disorder or the tail of a continuously distributed trait in the population. A recent large twin study reported high heritability of ADHD irrespective of whether continuum or categorical approaches were used or if different cut-off criteria were applied (Levy *et al*. 1997). A continuum approach, therefore, does not argue against heritability but argues for the inheritance of a trait rather than a disorder. The DSM-IV and many other clinical approaches are categorical, but the requirement of specific numbers of symptoms for a diagnosis seems to be arbitrary and may be artificially imposing a categorical construct. An argument against the continuum approach has been that it leads to diagnostic and therapeutic nihilism. This does not have to be so, as is evidenced by certain other clinical constructs such as anxiety. A longitudinal approach to the examination of genetic and environmental factors is necessary to further the continuum *versus* category debate, and adult ADHD should be studied in this context without restricting the examination to those meeting some arbitrary diagnostic criteria.

The focus on genetics has not been to the exclusion of possible environmental factors, a variety of which have been implicated: low socio-economic status, parental discord/divorce, neglect or abuse in childhood, early loss or separations, caregiving factors (intrusiveness at 6 month, overstimulation at 24–42 months) (see review by Cantwell, 1996). There may additionally be factors – genetic or environmental – that are protective, but these have received less attention.

Since attention and motor activity have neurobiological underpinnings that are beginning to be understood, there has been much interest in neuroimaging studies of ADHD to establish specific abnormalities that may not only act as markers for the disorder but also suggest pathophysiological mechanisms. Some of these studies have been in adults. Of the studies examining brain structure, the magnetic resonance imaging (MRI) studies are worthy of note although the findings are preliminary and their functional relevance unclear. Hynd and colleagues (1991, 1993) reported reduced volume of the right frontal cortex, the corpus callosum and the left head of the caudate nucleus in ADHD patients. Castellanos *et al*. (1994) reported a loss of normal caudate volume asymmetry and a 5% reduction in brain volume in boys with ADHD, and the same group reported corpus callosum abnormalities (Giedd *et al*. 1994). The functional imaging studies have generated even greater interest. Cerebral blood flow studies using single photon emission computed tomography (SPECT) demonstrated frontal and striatal abnormalities in children with ADHD (Lou *et al*. 1989, 1990). The first demonstration of abnormal cerebral metabolic rates in adult ADHD patients was by Zametkin and colleagues (1990), who reported reduced glucose metabolism using positron emission tomography (PET) in frontostriatal, somatosensory and occipital regions. The same group (Zametkin *et al*. 1993) could not replicate these findings in adolescents with ADHD. Studies examining the effect of stimulant drugs on cerebral metabolism in ADHD have also been largely negative (Matochik *et al*. 1993, 1994). Overall, the neuroimaging studies provide some interesting findings that need further elaboration before they can help categorize the disorder and provide insights into its pathophysiology. Recent neurological and neuroimaging studies have provided interesting insights into the neurobiology of attentional systems which may yield models for the understanding of ADHD (Voeller, 1991).

Electroencephalographic (EEG) studies, which have included brain mapping and the study of evoked responses, have yielded interesting group characteristics in children with ADHD (Levy & Ward, 1995), but questions remain about the diagnostic applicability of the EEG parameters. In particular, the ability of EEG data to predict treatment response warrants further investigation (Suffin & Emory, 1995). EEG studies are lacking in adults with ADHD. This has apparently not dissuaded a number of clinicians to use EEG data for diagnostic assessment and prognostication, an exercise without a definitive scientific basis. Systematic work in the utility of EEG and event-related potentials in adults with ADHD is urgently needed to guide clinical practice. Neuropsychological assessments of adult ADHD are few, and while the Continuous Performance Test (Rosvold *et al*. 1956) in its various forms is widely used in clinical practice, its validity remains to be established in adults.

The use of drugs in the treatment of ADHD has generated much interest in the neurobiochemical

basis of the disorder. A review of the literature suggests, however, that this field has remained speculative, with the various recent developments adding to the complexity without providing cogent new avenues of understanding (Rogeness *et al*. 1992). The focus remains on the catecholaminergic system, with dopaminergic mechanisms likely to be pre-eminent (Ernst & Zametkin, 1995). The recent genetic findings implicating the dopamine transporter and receptor genes, as described above, have provided further support for dopaminergic involvement. Dopamine depletion in neonatal rats, especially in the frontal cortex, produces hyperactivity that has some characteristics of the hyperactivity of ADHD, responds to stimulant treatment and usually abates after puberty (Shaywitz *et al*. 1976*a*, *b*). Knockout of the dopamine transporter gene in mice produces incessant hyperactivity (Giros *et al*. 1996). Norepinephrine depletion in neonatal rats produces deficits in learning without hyperactivity, and this has been suggested as a model for the inattentive form of ADHD (Shaywitz *et al*. 1984). The role of α2-noradrenergic function in prefrontal cortical cognitive function is well-documented, and its abnormality may play a role in ADHD (Arnsten *et al*. 1996). Serotonin deficiency has also been suggested as a possible neurochemical basis, especially of impulsivity and aggressiveness (Coccaro *et al*. 1989). The suggestion that seems to emerge from these findings is that while dopamine is important, the role of other amines, and their interactions, should also be considered to explain all the features of ADHD. Moreover, genetic influences are probably mediated through neurochemical changes and both aspects should continue to be investigated.

The longitudinal studies of childhood ADHD suggest continuation of symptoms, development of other psychiatric disorders, and educational, social and occupational disadvantage in adulthood (Klein & Mannuza, 1991; Fischer *et al*. 1993; Mannuza *et al*. 1993), thereby providing predictive validity for the syndrome. Similar studies have not been conducted for adults. Since early adulthood in such individuals is usually marked by significant psychopathology, it is likely that such dysfunction will persist into at least middle adulthood. Many controlled investigations have reported that adult ADHD responds to medication, in particular stimulant drugs which have been investigated in two open and six controlled investigations (see review by Wilens *et al*. 1995). The percentage of patients responding varied from 25% (Mattes *et al*. 1984) to as high as 78% (Spencer *et al*. 1995), in comparison with the 70% response rate usually reported in children. Can these data be construed as evidence of predictive validity of the syndrome in adults? These studies demonstrated a clear superiority of stimulant medication over placebo, but we still do not have data on the effect of similar doses of drugs on normal individuals. The widely accepted notion that stimulants produce a paradoxical effect on hyperactivity and attention in ADHD individuals was not supported by at least one investigation that examined the effect of dextroamphetamine in prepubertal boys and normal adult males (Rapoport *et al*. 1980). The normal individuals, not unlike those with ADHD, demonstrated decreased motor activity and improved cognitive functioning in response to the stimulant drug. This study, as it awaits replication, cautions us against the use of response to drug challenge as supportive evidence for a clinical diagnosis in an individual patient.

In conclusion, there are many pointers to the validity and clinical utility of ADHD in adults, but the diagnosis continues to pose problems to the taxonomist and the clinician. Further attempts at its validation are necessary if we are to determine its place in future psychiatric classifications, and develop effective treatments. A suitable strategy would be the longitudinal study of a large cohort of ADHD children well into adulthood, with comparison populations of children with anxiety disorders and conduct disorder without ADHD. This strategy, provided large enough cohorts are recruited, has the best possibility of providing groups of subjects who can be given the diagnosis which would be conceptually as well as clinically acceptable. They can also provide indicators to differentiate ADHD from co-morbid disorders, establish the longitudinal course of inattention, hyperactivity and impulsivity as distinct entities, and be the basis for neurobiological and genetic investigations. The ultimate goal, of course, is to be able to make the diagnosis in adults for the first time with considerable confidence. Since longitudinal studies are slow in yielding tangible results, epidemiological investigations of attentional disorders in adult populations must be carried out to determine the prevalence of adult ADHD. The features of inattention due to neurodevelopmental

causes must be distinguished, if possible, from inattention caused by injury to an adult and mature brain. Attempts to elucidate the neurobiological basis of ADHD, using genetic, electrophysiological and neuroimaging strategies, must proceed in both adults and children, but since the disorder is still best understood in children, the findings in adults should be consistent with those seen in children. Since childhood ADHD may well mature into disorders other than adult ADHD, e.g. as personality or affective disorders, the relationships of these disorders in adults to ADHD must be investigated using clinical and biological indicators. The study of co-morbid ADHD therefore assumes special importance and should not be dismissed as being 'too difficult to study'. A time may well come when the validity of ADHD in adults is well-established or advances in genetics or neurobiology have illuminated the genesis of attention deficit sufficiently to make other kinds of validation unnecessary. Until then, our use of the concept of adult ADHD should proceed with cautious scepticism lest our clinical zeal outpaces scientific credibility.

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