ogy, we examined the rates of depressive symptoms in children ($N = 1{,}056$) referred to the University of Chicago Hyperactivity, Attention, and Learning Problems Clinic between 1990 and 1997. In this data set, we examined a single, parent-report measure of depressive symptoms, using the cutoff score similar to that used by Biederman et al. (1993, 1996). With a CBCL Anxiety/Depression factor cutoff score ($T > 65$), 40.56% of all children with ADHD had statistically significant ratings on the Anxiety/Depression factor. This compared with 38.24% of the children with ADHD predominantly inattentive type and 26.24% for those children with psychiatric disorders other than ADHD. Consistent with Biederman et al. (1993), these data alone suggest a high degree of comorbidity between ADHD and depressive symptoms when parent-report data are used. However, when diagnoses were based on multidisciplinary consensus after a 6-hour evaluation which included semistructured diagnostic interviews with the parent and child by a child and adolescent psychiatrist or psychologist and review of all sources of information by 3 experienced clinicians, much lower prevalence rates for affective disorders were obtained. Specifically, 5.6% of the children with ADHD, 11% of children with ADHD predominantly inattentive type, and 5.3% of those with psychiatric disorders other than ADHD had comorbid major depression or dysthymic disorder.

We recognize these findings may be limited because interrater reliabilities of categorical diagnoses were not obtained and the diagnostic interview that was used has not yet been standardized. Nonetheless, the Chicago data suggest that the comorbidity of ADHD and depression is relatively modest and remarkably similar to the comorbidity found in clinic-referred children without ADHD.

On the basis of our data, we would agree with Dr. Biederman that empirical research is needed to clarify whether these children have "bad ADHD" or meet some other diagnostic criteria such as early-onset bipolar disorder. However, we must respectfully disagree that the controversy over the comorbidity of ADHD and bipolar disorder in children is merely a nosological issue. There is a fundamental methodological issue that demands careful attention. For now, simply relying on single-source reports of symptoms that are shared between ADHD and childhood bipolar disorder is insufficient. Until it has been demonstrated that children with ADHD actually do have a high risk for bipolar disorder, investigators and practitioners should be conservative in their approach to the diagnosis and treatment of these patients.

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NUTRITIONAL SUPPLEMENTS IN ADHD

To the Editor:

I read with great interest Dr. Heimann's letter (1999) on pycnogenol in the treatment of attention-deficit hyperactivity disorder (ADHD). I have treated more than 100 patients with ADHD, using nutritional supplements similar to pycnogenol (pine bark extract). His letter prompted me to share my experiences with your readers; I hope this letter will further discussion.

The biologically active compounds found in pycnogenol are oligomeric proanthocyanidins (OPCs). The use of OPCs for the treatment of ADHD has been circulating among parent groups, multilevel marketing companies, and Internet groups for at least 6 years. I became interested in these compounds after a treatment-resistant patient showed significant improvement without medications. Over the past 4 years I have recorded case studies demonstrating (1) EEG changes,(2) handwriting improvements, (3) improved school performance, and (4) continuous performance testing improvements. Family reports have ranged from no change to dramatic changes. There are few side effects of OPCs, although some children become irritable and have decreased energy. I have found the most significant improvements noted by patients are in areas relating to sustained attention and distractibility, rather than hyperactivity and impulsivity.

OPCs are one class of flavanoids. Flavanoids are a ubiquitous group of polyphenolic substances which are present in most plants. OPCs have been isolated from many plants including apples, berries, grapes, raspberries, and blackberries, and they are also present in many red wines (Schwitters and Masquelier, 1995). Although OPCs were originally extracted from pine bark, pine bark (pycnogenol) is significantly more costly than extracts from other plant materials. In my practice I have found that patients taking grape seed extract or OPCs from many different sources have more consistent responses.

How OPCs improve brain function and possibly symptoms of ADHD is speculative. The simplest explanation may involve the protective effects of proanthocyanidins on brain lipid peroxidation. There are animal models that have demonstrated this effect with grape seed extracts (Bagchi et al., 1998). Free radicals have been implicated in a number of disease processes including asthma, cancer, cardiovascular diseases, cataracts, diabetes, macular degeneration, Parkinson disease, and many other inflammatory processes. The brain

may be particularly vulnerable to free radical damage because neurons are so rich in docosahexaenoic acid (DHA), a highly polyunsaturated fat. Unfortunately, as Dr. Heimann pointed out in his letter, there are not any published studies of ADHD and OPC, either alone or combined with other treatment strategies.

There is a rapidly expanding body of literature on nutrition and brain function. The research is embedded in nonclinical journals, and headlines are quickly picked up by the unregulated health food industry. Hence, the "miracle cure" of the week is discovered. Nutritional claims in the treatment of ADHD have a long history of parents and professionals taking sides. Diet fads and "alternative" therapies come and go as parents desperately seek help. Nutritional biochemistry and the understanding of cellular metabolism is not alternative medicine, but the foundation for health and all disease processes. Medicine has slowly embraced nutritional research. Psychiatry has lagged far behind. The benefits of nutritional supplementation have quietly penetrated such conservative medical publications as the *New England Journal of Medicine* (Oakley, 1998).

Diet has been associated with many major chronic illnesses. The research is quite clear that lifestyle choices including dietary habits affect our genetic potential. Many of my colleagues dismiss the role of nutrition in ADHD, quoting old negative studies on food additives, sugar, and megavitamin therapy. A 1997 study published in *Pediatrics* found only 1% of children and adolescents met recommended dietary allowances, with 50% of daily calories from fat and sugar (Munoz et al., 1997). A study published in this *Journal* found that food insufficiency and hunger are associated with poor behavioral and academic functioning (Murphy et al., 1998). Is it such a leap of scientific faith to surmise that the incredibly complex neurochemistry that controls our ability to pay attention may need a sufficient supply of nutrients for optimal functioning?

ADHD is a complex, multifaceted disorder that disrupts psychosocial development and may have profound consequences in every aspect of a child's life. Understanding ADHD as a genetic neurobiological disorder or "chemical imbalance" might provide an explanation for parents giving their children psychotropic medications, but it does not explain the tremendous variability of symptoms, nor the treatment success many of us have had with OPCs and other nutritional interventions.

In my psychopharmacology practice, I have had clinical success in treating children and adults with ADHD by utilizing OPC, adjusting protein-carbohydrate ratios, and supplementing with trace minerals and specific fatty acids based on a detailed red blood cell membrane analysis from Kennedy Krieger Institute in Baltimore. OPCs are safe, naturally occurring, nontoxic compounds that might cost families a few cents a day. Clinical trials are desperately needed to begin a scientific understanding of these exciting case studies. I hope that funding can be found for an unpatentable compound that might not provide a significant income for a pharmaceutical company, but might provide an effective biological alternative for many patients.

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Comment by Dr. Horrigan, at the invitation of the Editor:

Antioxidants are now recognized as safe and effective treatments for clinical entities encountered by psychiatrists such as traumatic brain injury, tardive dyskinesia, and Alzheimer's type dementia (Felician and Sandson, 1999; Inci et al., 1998). The key mechanism appears to be the prevention of further cell membrane damage (and consequent cell death) via the neutralization of free radicals such as those generated by nitric oxide (Wallis et al., 1996). Vitamin E is the most widely publicized agent in this regard. There are no definitive studies that have described cell death as an etiological or exacerbating factor in ADHD as defined by *DSM-IV*.

Antioxidants vary in terms of potency as well as bioavailability when ingested orally. Pine bark extract is purported to be superior to both vitamin E and C in each of these areas. However, given that antioxidants (including pine bark extract) are marketed in America without formal Food and Drug Administration oversight, the actual content of any over-the-counter "antioxidant" is generally unknown (although it is true that some manufacturers are more reputable than others).

Nutritional interventions are also well recognized and have been incorporated into clinical and research endeavors of psychiatric medicine. One example is the routine use of tryptophan-depletion protocols in studies that examine the role of central serotonin (5-HT) levels in psychiatric disorders (Reilly et al., 1997). Tryptophan is an essential amino acid that can be obtained only through the diet, and it serves as the precursor to 5-HT. Tryptophan-free protein drinks represent a relatively rapid way to decrease central levels of 5-HT.

The field of child and adolescent psychiatry, as well as medicine on the whole, would be greatly enriched if Dr. Greenblatt opted to present his findings systematically. Public exposition of his data, with proper statistical analyses, would thus allow the reader to draw independent conclusions concerning the