Professor Basant K Puri's Medical School Talk – Part IV
Attention-Deficit Hyperactivity Disorder

by **Albert Cilia-Vincenti** *MD FRCPath*

Increasing numbers of children are being diagnosed as having ADHD. The best available treatment has been powerful drugs that help control, but not cure, the worst symptoms. The potential side-effects of these drugs are worrying and the long-term consequences unknown, facing doctors, parents and adult sufferers with a dilemma. Professor Puri looks at ADHD in a different way, starting with brain chemistry and the factors that may influence this. He presents the results of two major studies with which he has been involved and that demonstrate the effectiveness of a completely natural treatment.

There are several theories about the causes of ADHD and why more people seem to have it. A number of these theories imply that it is not really a medical illness, but may be due to bad parenting, lack of discipline in modern schools, break-up of families, loss of communal religious practice and social cohesion, and to the way our lives have become more complicated and stressful.

Basant Puri's research has shown that ADHD is associated with clear-cut changes in body chemistry which, when treated in a completely natural way, will improve the symptoms and actually cure the disorder, proving that it is a genuine medical illness. Current conventional treatment consists of some form of therapy with powerful psychostimulants such as methylphenidate (Ritalin®) and amphetamine (Adderall® and Dexedrine® - marketed in UK but not in Malta). Many parents of children with ADHD, or adult ADHD sufferers, do not wish to use these powerful drugs, and may not seek help for this reason. Thus many people with this condition, particularly adult sufferers, may not be recognised.

By the 1990s, American schools were reporting many children queuing up every day for stimulant anti-ADHD medication. The increases in production and use of methylphenidate in the US (figure 1) are even more striking when compared to worldwide date (figure 2). In the UK, the National Institute for Clinical Excellence (NICE) has estimated that in a class of 30 pupils, on average one or two children will have ADHD, while in every three classes one child will have severe ADHD (hyperkinetic disorder). True figures might be much higher if many children have indeed not been correctly diagnosed.

ADHD carries enormous financial,

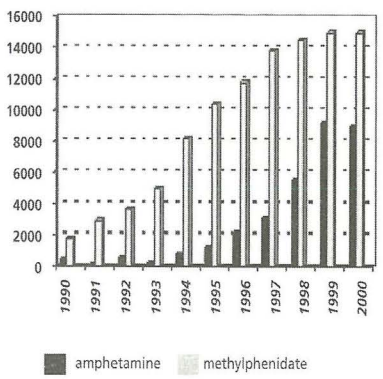

Figure 1: *Aggregate production quota in kilograms.*

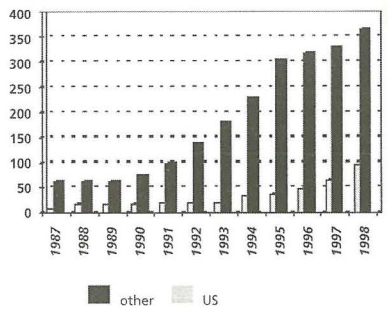

Figure 2: *Daily methylphenidate dose in millions of prescriptions.*

social and emotional costs, such as extra specialised school staff, extra home childcare, failure in fulfilling career potential, stress on marriages, educational system burden, in trying to cope with classroom disruptive behaviour, and the individual medical consequences of the stress on the lives of parents and teachers.

Modern research, largely sponsored by pharmaceutical companies, does indicate that this illness has biological causes. Brain neurotransmitters have been found to be abnormal in ADHD. However, the use of psychostimulants came first, and attempts to provide scientific 'justification' for their use followed later. These drugs have helped many children with ADHD, but they carry the risk of unpleasant side-effects. Methylphenidate has similar behaviour to amphetamines – would you give a child some amphetamine or cocaine and not expect unpleasant reactions?

New non-stimulant drugs are being developed for ADHD, the first being atomoxetine hydrochloride (Strattera®), but there are already reports of adverse reactions, including abnormal LFTs, jaundice and hepatitis, with these new drugs. Some parents have therefore turned to the complementary/alternative medicine sector. Avoiding artificial colourings and sweeteners certainly helps, but until Puri's research, there was no scientifically convincing evidence that alternative treatments actually worked.

The cardinal features of ADHD are inattention, hyperactivity and impulsiveness. Different levels of each of these features can appear in different individual sufferers and within each feature, there will likely be differences in the type and/or degree of the symptoms and signs. There are also gender differences, with boys being about 2½ times as likely as girls to suffer from ADHD.

ADHD needs to be differentiated from other disorders, such as autism spectrum disorder, an anxiety disorder or depression, adrenoleucodystrophy (genetic disease affecting males and characterised by abnormal adrenal cortex and brain white matter), and a conduct disorder. The latter is the most difficult to differentiate from ADHD, and some researchers suggest it may be a complication of ADHD. Furthermore, anxiety, depression or a conduct disorder often co-exist with ADHD.

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Specific learning or language difficulties also tend to co-exist with ADHD, as does developmental coordination disorder, also known as dyspraxia ('minimal brain damage'/'clumsy child syndrome'). Tic disorders may also co-exist with ADHD, and these may take the form of repetitive movements or sounds. Some people with ADHD also appear to have a predilection for abusing illegal drugs. Overall, delays in achieving reading skills or proper motor co-ordination can make it increasingly difficult for affected children to socialize.

Although ADHD and hyperkinetic disorders are currently commonly diagnosed, this was not case until the second half of the 20th century. In 1934, Eugen Kahn and Louis H Cohen described hyperactive (and intelligent) children and adults, and proposed this was caused by a brain stem organic disorder, but this theory did not stand the test of time[1]. Researchers are now more likely to think that the cerebral cortex is more important than the brain stem in causing ADHD.

In 1918, Walter Dandy (professor of neurosurgery at Johns Hopkins, succeeding Harvey Cushing) discovered how to X-ray image the brain ventricles by replacing the CSF with air, a side-effect of which was headaches[2]. Charles Bradley thought Benzedrine® (amphetamine sulphate) might stimulate the brain to produce more CSF after pneumoencephalography to help ease the headaches[3]. He was wrong, but hyperactive children who had been given Benzedrine after this procedure were noted to find it easier to sit still and concentrate in class and, in 1937, he reported that out of 30 children with behavioural problems, 14 showed a 'spectacular change in behavior' and 'remarkably improved school performance'. This is the real foundation for amphetamine and amphetamine-like drugs in children with ADHD.

Neurons communicate via neurotransmitters, which include dopamine, noradrenaline, serotonin, gamma-amino butyric acid (GABA) and glutamate (glutamic acid). Benzedrine® and Ritalin® release dopamine into the synaptic cleft and possibly stop it being removed (figure 3). There is an important pathway containing dopamine brain cells which starts from the brain stem ventral

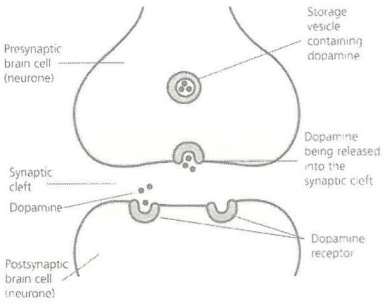

Figure 3: *Dopamine neurotransmission*

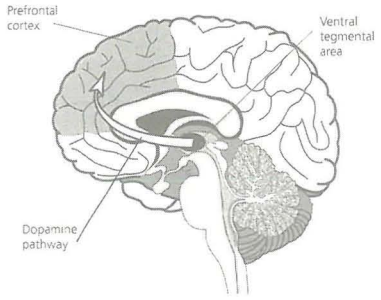

Figure 4: *Dopamine pathway*

tegmental area and reaches forward to innervate parts of the frontal lobe and limbic system. The dorsolateral prefrontal cortex may contain some of our 'free will' circuits. The limbic system processes the sense of smell, emotions, learning and memory. The dopamine pathway (figure 4) also innervates the medial prefrontal cortex (mesocortical system). These pathways may also mediate attention, arousal and concentration. Psychostimulants are recommended for ADHD because of their alleged beneficial action on this dopamine pathway.

Genes related to dopamine transmission have also been found to be abnormal in ADHD, but the abnormalities described account for only a tiny fraction of the total genetic component to ADHD. Dopamine is key to pleasure perception. Pleasure centres form part of the brain reward system. ADHD patients have an abnormal brain reward system, making decisions to maximise immediate reward, while ignoring the medium to long-term. Such a 'reward deficiency syndrome' has also been blamed for addiction and pathological gambling. Deficiency of internal brain rewards may instigate seeking substances (alcohol, tobacco, illicit drugs), or behaviours (over-eating, gambling or sexual promiscuity) that release dopamine in brain pleasure centres.

Puri's research into the role of fatty acids in health and disease has led him to the conclusion that many conditions, including ADHD, result from fatty acid deficiencies. The fatty acid model of ADHD[5], put forward by Alex Richardson and Basant Puri in 2000, proposed that at least some features of ADHD may reflect an underlying abnormality of fatty acid metabolism. Viruses, saturated fats, hydrogenated and trans fats, vitamin and mineral cofactor deficiencies, stress hormones and excessive alcohol, can also interfere with fatty acid metabolism.

Production of omega-3 and omega-6 fatty acids influences brain development, including neuronal migration and branching, nerve fibre growth, and the creation, remodelling and pruning of neuronal connections. Fatty acid metabolism defects affect neuronal communication, resulting in cognitive defects or problems with thought processes, such as short-term memory, and attention and concentration, as in ADHD. Abnormalities of dopamine neurotransmission may be involved in ADHD, but the function of all neurotransmitters and their receptors are influenced by the lipid content of the membranes within which those receptors lie. Zimmer and colleagues showed in 2002 that omega-3 fatty acid deficiency in rats is related to dopamine pathway changes resulting in a less active mesocortical system[6]. This confirms that omega-3 deficiency plays a role in impaired dopamine neurotransmission in ADHD. Thus, in the Richardson and Puri fatty acid model of ADHD, ***the fatty acid abnormalities are primary, while the neurotransmitter changes, including dopamine neurotransmission abnormalities, are secondary***.

Mitchell and colleagues, in 1987, compared 48 hyperactive children with 49 normal controls, and found a lower average birth weight and blood omega-3 and omega-6 fatty acids in hyperactive children[7]. Laura Stevens and John Burgess, in 1995, described reduced blood and red cell membrane levels of omega-3 fatty acids in 53 boys with ADHD when compared with 43 normal controls, suggesting a difficulty in converting fatty acid precursors into long-chain polyunsaturated fatty acids such as EPA (*eicosapentaenoic acid*)[8].

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In 1996, the Laura Stevens group found that children with specifically low omega-3 fatty acid levels scored significantly lower on mathematics and overall academic ability. Also in 1996, Bekaroglu and colleagues found significantly lower fatty acid and zinc blood levels in 48 children with ADHD[9]. A lack of zinc can inhibit the omega-3 and omega-6 metabolic pathways. In 2004, Jiun-Rong Chen and colleagues studied 58 children with ADHD and found they had lower omega-3 fatty acid levels compared to normal controls in spite of similar diets, again suggesting a possible problem with essential (short-chain) fatty acids conversion into the long-chain polyunsaturated fatty acids[10]. Also in 2004, Young and colleagues found similar fatty acid results in adult ADHD to those found in childhood ADHD[11].

Ross and colleagues, in 2003, found higher ethane (breakdown product from oxidative damage to omega-3 fatty acids) in exhaled breath of ADHD patients. The evidence for ADHD patients having difficulty synthesizing long-chain polyunsaturated fatty acids, together with evidence that what they can synthesize is broken down too quickly, suggest that the appropriate treatment for ADHD might be supplementation with long-chain polyunsaturated fatty acids.

Several trials of long-chain polyunsaturated fatty acids have taken place. Harding, Judah and Gant showed that huge daily dietary supplementation with vitamins, minerals, amino acids and fatty acids was just as effective as methylphenidate in alleviating ADHD symptoms, but Basant Puri ***does not recommend children or adults with ADHD to take such high doses of vitamins and minerals, some of which, like vitamin A and chromium, might be toxic at those levels***.

Supplementation with evening primrose oil only, or with DHA (omega-6 long-chain polyunsaturated fatty acid docosahexaenoic acid) only, are both ineffective. Furthermore, DHA may have detrimental effects on ADHD symptoms. Richardson and Puri, Richardson and Montgomery, and Portwood, Lowerson and Puri, have shown that EPA with evening primrose oil is an effective way to alleviate ADHD symptoms.

Unfortunately, the regimes used in these studies included DHA. ***DHA is considered not only detrimental to ADHD symptoms, but too much DHA in supplement form may be carcinogenic in the long-term, and should therefore be avoided in supplements***. An over-the-counter supplement is now available (also in Malta) that contains pure EPA, unrefined evening primrose oil and ***no*** DHA.

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Professor Cilia-Vincenti is a former London University Teacher of disease mechanisma at Charing Cross and The Middlesex Hospital medical schools, and at the Malta medical school. He is currently steering group chairman of the Academy of Nutritional Medicine based in Cambridge, UK. He may be contacted on *acvincenti@onvol.net*.