Mastering Migraine – Making Meaning of the message

By Michael McIntyre

Migraine is the commonest functional disorder suffered by patients with about 10% of the population suffering regular attacks.[1] There is a dramatic difference in incidence between the sexes with three women to every one man suffering from this affliction.[2] Cluster headaches are the exception, being commoner in men than in women. Migraine is now ranked 19th by the World Health Organization in its categorisation of diseases causing disability on a world-wide basis. About 80 percent of people who have migraine headaches have a family history of migraines.

The term migraine comes directly from the old French which itself is derived from the Greek *hemi* = half and *kranion* = skull. Old English = *megrim*

Signs and symptoms

Although the word migraine describes a one-sided recurrent headache, pain is not the only characteristic of a migraine which can include a variety of symptoms. Sometimes migraine can occur without head pain e.g. with aura only or stomach migraine.

- Recurrent headache manifesting in attacks lasting 4-72 hours.
- Typically unilateral but migraine headache is commonly bilateral in young children; an adult pattern of unilateral pain usually emerges in late adolescence or early adult life.
- Moderate to severe pain often with pulsating (throbbing) quality,
- Aggravated by physical activity (movement)
- Nausea and vomiting
- Photophobia and phonophobia
- Hyperacusis
- Approximately one third of sufferers experience preceding visual aura or other physical changes such as sensory loss or olfactory distortion.
- Hyperactivity or lassitude
- Depression or elation (mood changes)
- Craving for particular foods,
- Repetitive yawning

NB The headache and other symptoms should not be attributed to another disorder.

Migraines are classified into various categories.

- **Migraine with aura (classic migraine) -** headache heralded by an aura. People who get migraines with aura sense when an attack is coming on and the aura typically presents as a scintillating scotoma - a flickering

[1] Obermann M, Katsarava Z. Epidemiology of unilateral headaches. *Expert Rev Neurother*. 2008 Sep;8(9):1313-20.

[2] http://womenshealth.about.com/cs/headaches/a/migranes1.htm (accessed 3/11/08)

light in the centre of the visual fields, which then expands and may take the form of a zig-zag pattern, sometimes called a “fortification spectrum” because of its resemblance to the battlements of a castle. This phenomenon leads to gradual loss of part of the visual field (scotoma). Researchers suggest Lewis Carroll was actually a migraineur and the visual aura he suffered is said to have given him the idea of the disappearing Cheshire cat.

- **Migraine without aura (common migraine)** – characterised by headache and nausea is the commonest type of migraine. It is more frequent and is usually more disabling than migraine with aura.
- **Abdominal migraine (AKA stomach migraine) -** regular attacks of acute abdominal pain that lasts from one to two days in the absence of any other digestive cause. May bring on nausea and vomiting. Between attacks the individual is healthy and completely symptom free. Often observed in children.
- **Cluster headaches**- Attacks of severe, unilateral pain which is orbital, supraorbital, temporal or in any combination of these sites, lasting 15-180 minutes and occurring from once every other day to 8 times a day. The attacks are associated with one or more of the following, all of which are ipsilateral:, lacrimation, nasal congestion, rhinorrhoea, forehead and facial sweating, miosis and ptosis. Patients are restless or agitated during an attack.
- ***Status migrainosus*** is a rare and severe type of unrelenting migraine that can last 72 hours or longer. The pain and nausea are so intense that people who have this type of headache are usually be hospitalized. The use of certain drugs can trigger *status migrainosus*. Patients in *status migrainous* are at increased risk of stroke.
- **Menstrual migraines** Fluctuating hormone levels appear to be related to migraine. Menstrual migraine affects approximately 50% to 60% of female migraineurs[3]. Three quarters of adult migraine patients are female.[4]
- **Medication-overuse headache** –Excessive use of common medications for treatment of acute migraine (opioid and nonopioid analgesics $5HT_1$ agonists, ergotamine and caffeine) are associated with medication-overuse headache. The headaches are likely to occur during drug withdrawal and also often occur first thing in the morning as the person has effectively withdrawn from the drug overnight.

Aetiology of migraines

The aetiology of migraines was a matter of conjecture amongst physicians since well before the time of Hippocrates who himself puzzled over its nature and cause. Ancient Greek doctors proposed that an excess of yellow or black bile (melancholia - μέλας, *melas*, "black", + χολή, *kholé*, "bile) were the cause of such headaches. With the advent of brain imaging, the last twenty years has seen

[3] Brandes JL. The influence of estrogen on migraine: a systematic review. *JAMA.* 2006 Apr 19;295(15):1824-30.
[4] . http://www.achenet.org/education/patients/MigraineinWomen.asp (accessed 3 Nov 08)

remarkable advances in getting to grips with the pathological processes that trigger migraine attacks (see research paper 1 below) The following is a summary of current ideas of the pathogenesis of migraines.

1. Vasogenic theory

- It used to be thought that the aura and then headaches in migraines were caused solely by blood vessels first contracting and then dilating in the brain (*vasogenic theory*). This theory assumed that the aura phase of migraine was due to ischemia induced by transient vasoconstriction and that the headache phase was caused by a rebound vasodilation, which mechanically activated primary nociceptive axons within the walls of engorged cerebral vessels. Whereas most of the brain is insensitive to pain, meningeal blood vessels are richly supplied with nerves. Blood vessel dilation activates the trigeminal sensory nerves that surround the meningeal blood vessels, causing pain. Activation of trigeminal nerves also causes the release of vasoactive neuropeptides (see 3 below) that further contribute to dilation and worsen pain.

- Evidence for this hypothesis was supported by studies that noted the occurrence of oligaemia during the aura phase of a migraine and an increase in blood flow during the headache phase. The blood vessel theory of migraine seemed to be further validated because when a patient with a headache is given a vasodilator such as a nitrate, the headache intensifies, whereas when a patient is given a vasoconstrictor such as a 5-HT agonist or ergotamine, the headache is usually alleviated. However, researchers have questioned whether the decreases in cerebral blood flow during the aura phase are sufficient to cause the aura symptoms (e.g. visual disturbances). Furthermore, vasodilation alone cannot explain the local swelling and tenderness of the head that generally accompany migraine.

2. Neurogenic theory

- Brain imaging suggests that migraine symptoms are provoked by brain excitability - changes in the activity of neurons (*neurogenic theory*). Patients with migraines exhibit *cortical spreading depression (CSD),* self-propagating waves of cellular depolarization that spread across the surface of the brain. According to the neurogenic point of view, the decrease in blood flow that takes place during migraine aura is seen as the direct consequence of reduced metabolic demand in abnormally functioning neurons and not the primary cause of the symptoms of aura. Thus CSD is proposed as the cause of migraine aura.[5] Some

5 Milner P. Note on a possible correspondence between the scotomas of migraine and spreading depression of Leao. EEG Clin Neurophysiol. 1958;10:705.

researchers now postulate that CSD may trigger not only the aura of migraine but the pain and nausea common in migraine patients. This neurogenic theory is supported by clinical evidence that the symptoms of migraine aura spread beyond the boundaries of any single neurovascular territory.

- MRI studies of people with migraine have demonstrated an increased incidence of actual brain changes called white matter lesions (WMLs) in patients with migraine.[6] However, such WMLs are also found in people without migraine with 83% of people showing these changes in their seventies.[7] WMLs are localized in the posterior circulation and this would appear to correspond with studies that suggest that the cerebellum plays a role in the pathophysiology of migraines.[8] WMLs are known to be associated with other aetiologies than migraines such as diabetes, smoking raised cholesterol and high blood pressure and dementia.[9] People suffering regular migraines are approximately four times more likely than non-migraine subjects to have WMLs.[10] The evidence of ischaemic WMLs in migraineurs raises questions about whether migraine may be a progressive disorder rather than episodic in nature. Some investigators have reported that 2/3^{rds} of patients with migraines develop sensitisation – a form of progression of the disease that makes recurrence more likely.[11]
- The reduction in cerebral blood flow (CBF) during migraine and focal hypoperfusion may explain findings of other subclinical infarct-like brain lesions shown in several brain-imaging studies. It is postulated that CBF reduction triggered by CSD can affect some especially vulnerable regions of the brain, like the cerebellum, where, as mentioned, migraine related changes produce focal ischemic damage.[12]
- Migraine, especially occurring with aura, has also been associated with an increased prevalence of patent *foramen ovale*. The *foramen ovale* is a channel between the atria of the foetal heart allowing blood to flow from the right to the left atrium, which shunts oxygenated blood to the systemic circulation during foetal development. It is not needed in adult life when the lungs are functional, and should close after birth. Occasionally this fails to happen and a significant minority of adults have a patent *foramen ovale*. Patent foramen ovale (PFO) is associated with increased risk of stroke. In recent years it has also been associated with migraine. While

[6] Cutrer FM, Sorensen AG, Weisskoff RM, et al. Perfusion-weighted imaging defects during spontaneous migrainous aura. Ann Neurol. 1998;43:25-31.
[7] Fazekas F. Magnetic resonance signal abnormalities in asymptomatic individuals: Their incidence and functional correlates. *Eur Neurol.* 1989;29:164-168
[8] Harno H, Hirvonen T, Kaunisto MA, Aalto H, Levo H, Isotalo E, Kallela M, Kaprio J, Palotie A, Wessman M, Färkkilä M. Subclinical vestibulocerebellar dysfunction in migraine with and without aura. *Neurology.* 2003 Dec 23;61(12):1748-52.
[9] Ketonen LM. Neuroimaging of the aging brain. *Neurol Clin.* 1998 Aug;16(3):581-98.
[10] Swartz RH, Kern RZ. Migraine is associated with magnetic resonance imaging white matter abnormalities: a meta-analysis. *Arch Neurol.* 2004 Sep;61(9):1366-8.
[11] Yarnitsky D, Goor-Aryeh I, Bajwa ZH, Ransil BI, Cutrer FM, Sottile A, Burstein R. 2003 Wolff Award: Possible parasympathetic contributions to peripheral and central sensitization during migraine. *Headache.* 2003 Jul-Aug;43(7):704-14.
[12] Kruit MC, Launer LJ, Ferrari MD, van Buchem MA. Infarcts in the posterior circulation territory in migraine. The population-based MRI CAMERA study. *Brain*. 2005 Sep;128(Pt 9):2068-77. Epub 2005 Jul 8.

closing a large PFO to try and prevent stroke might make sense, cardiac surgery to prevent migraine, however bad, is difficult to justify.

- PET scans of patents with migraine have revealed an increase in CBF in the brainstem suggesting that there could be a “migraine generator" located within brainstem (see research paper 2 below).[13] [14] As mentioned, according to the neurogenic theory, vasodilation is not the primary cause of migraine headaches but is an accompanying phenomenon attributable to trigeminal nerve activation. The cause of this activation may be due to metabolic disturbances in brain function, such as those associated with anoxia (see paper 4 below), CSD and abnormal activity in brain-stem sensory nuclei which activate trigeminal sensory pathways to release pain provoking peptides (see section 3. below).

3. Neuropeptide theory

- A third aspect of migraine causation highlights the role of neuropeptides as pain promoters. As the central nervous system reacts to various factors such as bright lights or tiredness, nerve cells react by dilating the blood vessels in certain areas of the brain. When the blood vessels dilate, nerves in the walls of the blood vessels release potent pain neuropeptides (such as substance P, neurokinin A, bradykinin and Calcitonin-Gene Related Peptide - CGRP) from axon terminals into dural and meningeal blood vessels. Bradykinin and neurokinin A cause vasodilation whilst Substance P release in turn provokes mast cells to release histamine and platelets to release serotonin, with consequent vasodilation and exudation of plasma into the tissues. It also appears that nitric oxide is involved in this process. NO is an important messenger molecule involved in many physiological and pathological processes that can cause vasodilation and also acts as a nociceptive neurotransmitter. Although CGRP does not promote plasma extravasation, it is a potent vasodilator and pain promoter as is bradykinin, a major component of wasp stings.[15] Together, these neuropeptides and NO produce an inflammatory response in the area around the innervated blood vessels termed “*neurogenic perivascular inflammation*”. It is this that is thought to cause the throbbing pain of migraine headaches.

4. The serotonergic abnormalities hypothesis

- It has been observed that both plasma and platelet levels of serotonin (AKA 5-hydroxytryptamine, or 5-HT) fluctuate during a migraine attack suggestive that serotonin may be involved in the pathogenesis of migraine. In the body serotonin is synthesized from tryptophan and is naturally present in vegetables, plants like mushrooms, fruits, certain nuts

[13] Cooney BS, Grossman RI, Farber RE, Goin JE, Galetta SL. Frequency of magnetic resonance imaging abnormalities in patients with migraine. *Headache.* 1996;36:616-621.
[14] Fazekas F. Magnetic resonance signal abnormalities in asymptomatic individuals: Their incidence and functional correlates. *Eur Neurol.* 1989;29:164-168

[15] Mendes MA, Palma MS. Two new bradykinin-related peptides from the venom of the social wasp Protopolybia exigua (Saussure). *Peptides.* 2006 Nov;27(11):2632-9. Epub 2006 Jul 11

and venoms. Once in the body, it is metabolized and inactivated rapidly to its major metabolite, 5-hydroxyindoleacetic acid (5-HIAA). Serotonin is located in the intestinal wall, large blood vessels, and CNS. Studies show it is involved in sleep, memory processes, mood, body temperature, muscle contraction, hormone regulation, and depression. Many of the effective treatments for migraines are drugs that activate or block (agonists or antagonists respectively) the 5-HT receptor. Mediators produced by 5-HT include bradykinin and prostaglandins, which, as mentioned above, act on nerve terminals to cause pain, inflammation and sensitisation.[16] The development of sumatriptan, a 5-HT[1B/1D]-receptor agonist, has proved effective in the aborting the pain of migraine once it has begun. However, it seems unlikely that changes in blood serotonin levels are solely responsible for the development of migraine. For instance, global brain changes in plasma serotonin levels do not explain the unilateral nature of migraine pain.

- Increases in platelet activity and catecholamine levels and in serotonin release from the *dorsal raphe nucleus* occur in the early morning. Because these changes may trigger the trigeminovascular system (i.e.trigeminal innervation of the cranial blood vessels), either directly or through ischemia, this might partially explain the circadian rhythm of migraine (i.e. regularly occurring attacks).
- The *dorsal raphe* provides a substantial proportion of the serotonin innervation to the forebrain and REM sleep inhibits the release of serotonin from the *dorsal raphe nucleus*. This perhaps provides an explanation for the commonly found phenomenon that sleep may abort or alleviate a migraine attack. It would appear that it does this by inhibiting the serotonin-mediated stimulation of the trigeminovascular system.

5. Sympathetic system overload

- Stress is a commonly cited cause of and sympathetic activation is a primary component of the physiological stress response. It would appear that migraine attacks are associated with dysfunction of the sympathetic nervous system. It has been suggested that a migraine attack is characterized by a relative depletion of sympathetic norepinephrine stores in conjunction with an increase in the release of other sympathetic neurotransmitters such as dopamine, prostaglandins, adenosine triphosphate, and adenosine.[17] The sympathetic nervous system (SNS) overload hypothesis suggests that after prolonged or excessive SNS stimulation the relative synaptic concentrations of sympathetic neurotransmitters that cause vasoconstriction (i.e. norepinephrine) and that cause vasodilatation (i.e. dopamine, adenosine, prostaglandins) alter so that the net effect of SNS stimulation on the extracranial circulation is no longer vasoconstriction but vasodilatation (see research paper 7 below).

[16] Solomon GD, Lee TG & Solomon CS; (1998); *Clinician's Manual on Migraine*; Pub. Science Press, London

[17] Peroutka SJ. Migraine: a chronic sympathetic nervous system disorder. *Headache.* 2004 Jan;44(1):53-64.

- Increased sympathetic nervous activity in the intestine causes nausea, vomiting, and diarrhoea. Sympathetic activity also delays emptying of the stomach into the small intestine and thereby prevents oral medications from entering the intestine and being absorbed. The impaired absorption of oral medications is a common reason for the ineffectiveness of medications taken to treat migraine headaches during an attack. The increased sympathetic activity also decreases the circulation of blood, and this leads to pallor of the skin as well as cold hands and feet. Increased sympathetic activity also contributes to the sensitivity to light and sound sensitivity as well as blurred vision.

6. Female hormones

- The relationship between female hormones and migraine is still unclear. Women may have "menstrual migraine" - headaches around the time of their menstrual period - which may disappear during pregnancy. Other women develop migraine for the first time when they are pregnant. Some are first affected after menopause.
- The effect of oral contraceptives on headaches is also unclear. Some women with migraine who take the contraceptive pill experience more frequent and severe migraine attacks. However, a small percentage of women have fewer and less severe migraine headaches when they take birth control pills and women who do not suffer from headaches may develop migraines as a side effect when they use oral contraceptives.
- While female sex steroids do not seem to be directly involved in the pathogenesis of migraine, they may modulate several mediators and/or receptor systems within the central nervous system, as well as at the peripheral neurovascular level (see research paper 5 below)

Abstracts of some relevant research papers:

1. Functional neuroimaging of primary headache disorders.

"Until recently, primary headache disorders, such as migraine and cluster headache were considered to be vascular in origin. However, advances in neuroimaging techniques, such as positron emission tomography, single photon emission computed tomography and functional magnetic resonance imaging have augmented the growing clinical evidence that these headaches are primarily driven from the brain."[18]

2. New insights into migraine: application of functional and structural imaging

"Functional neuroimaging in headache patients has revolutionized our understanding of these syndromes. Further insights into the pathophysiology of headache syndromes have been provided by innovative neuroimaging analysis using structural data. This review highlights the recent advances made in studying migraine using

18 Cohen AS, Goadsby PJ. Functional neuroimaging of primary headache disorders. *Expert Rev Neurother*. 2006 Aug;6(8):1159-71.

neuroimaging techniques. Several independent studies have reinforced the crucial role for the brainstem in acute and probably also chronic migraine."[19]

3. Neuroimaging: enhanced understanding of migraine pathophysiology.

"Recently, newer imaging techniques have been providing noninvasive methods of studying metabolism and hemodynamics in the brains of migraineurs during and between acute attacks. 133Xe blood flow techniques, transcranial Doppler, and SPECT have all been employed to investigate hemodynamic changes during migraine aura. PET has been useful in the study of migraine without aura, with findings of increased blood flow related to pain in cortical areas and in the medial brainstem. Currently, three functional MRI imaging techniques are being used in migraine research…..Despite conflicting findings - migraine with visual aura appears to be generally associated with transient decreases in regional cerebral blood flow." [20]

4. Cortical spreading depression causes and coincides with tissue hypoxia.

"Cortical spreading depression (CSD) is a self-propagating wave of cellular depolarization that has been implicated in migraine and in progressive neuronal injury after stroke and head trauma. Using two-photon microscopic NADH imaging and oxygen sensor microelectrodes... we find that CSD is linked to severe hypoxia and marked neuronal swelling that can last up to several minutes. Changes in dendritic structures and loss of spines during CSD are comparable to those during anoxic depolarization. Increasing O2 availability shortens the duration of CSD and improves local redox state. Our results indicate that tissue hypoxia associated with CSD is caused by a transient increase in O2 demand exceeding vascular O2 supply."[21]

5. Potential role of female sex hormones in the pathophysiology of migraine

Clinical evidence indicates that female sex steroids may contribute to the high prevalence of migraine in women, as well as changes in the frequency or severity of migraine attacks that are in tandem with various reproductive milestones in women's life. While female sex steroids do not seem to be involved in the pathogenesis of migraine per se, they may modulate several mediators and/or receptor systems via both genomic and non-genomic mechanisms; these actions may be perpetuated at the central nervous system, as well as at the peripheral (neuro)vascular level. For example, female sex steroids have been shown to enhance: (i) neuronal excitability by elevating Ca(2+) and decreasing Mg(2+) concentrations, an action that may occur with other mechanisms triggering migraine; (ii) the synthesis and release of nitric oxide (NO) and neuropeptides, such as calcitonin gene-related peptide CGRP, a mechanism that reinforces vasodilatation and activates trigeminal sensory afferents with a subsequent stimulation of pain centres; and (iii) the function of receptors mediating vasodilatation, while the responses of receptors inducing vasoconstriction are attenuated. The serotonergic, adrenergic and gamma-aminobutyric acid (GABA)-ergic

19 May A, Matharu M. New insights into migraine: application of functional and structural imaging. *Curr Opin Neurol*. 2007 Jun;20(3):306-9. Review.

20 Cutrer FM, O'Donnell A, Sanchez del Rio M. Functional neuroimaging: enhanced understanding of migraine pathophysiology. *Neurology*. 2000;55(9 Suppl 2):S36-45

[21] Takano T, Tian GF, Peng W, Lou N, Lovatt D, Hansen AJ, Kasischke KA, Nedergaard M. Cortical spreading depression causes and coincides with tissue hypoxia. *Nat Neurosci*. 2007 Jun;10(6):754-62. Epub 2007 Apr 29.

systems are also modulated by sex steroids, albeit to a varying degree and with potentially contrasting effects on migraine outcome. Taken together, female sex steroids seem to be involved in an array of components implicated in migraine pathogenesis. Future studies will further delineate the extent and the clinical relevance of each of these mechanisms, and will thus expand the knowledge on the femininity of migraine.[22]

6. The pathogenetic bases of hemicrania

Studies of regional cerebral blood flow in migraine with aura have shown that the aura phase is associated with hypoperfusion in the cortical area which relates topographically to the clinical symptoms. Thus, the previously hypoperfused area becomes hyperperfused. However, there is no strict association between hyperperfusion and headache. The mode of hypoperfusion propagation recalls the circulatory manifestations of experimental cortical spreading depression. In addition, there are no focal cerebral blood flow abnormalities in migraine without aura. During the headache phase of migraine, dilation of both the large extra- and intracranial arteries takes place. A bulk of biochemical evidence has suggested that the pain in migraine is caused by blood vessels which are dilated and sensitized by circulating pain-producing substances e.g. bradykinin, serotonin and histamine (sterile inflammation). Recently, perivascular trigeminal fibres (trigeminovascular system) which, when stimulated, release sensory peptides (substance P and the calcitonin gene-related peptide) capable of provoking marked vasodilation and plasma extravasation (neurogenic inflammation) have been identified. Thus, the activation of the trigeminovascular system is probably involved in the vasodilatative and nociceptive phenomena of the migraine attack. The finding of a reduced endorphinergic brain tonus in migraine patients supports the hypothesis of a central nociceptive derangement in migraine. Nonetheless, the exact relationship between vasodilation and headache remains to be defined. However, the potent antimigraine effectiveness of sumatriptan--an agonist of the serotonin receptors which selectively constricts dilated arteries during the migraine attack--once again stresses the fact that serotonin is probably the crucial factor in the link between vasodilation and headache[23]*.*

7. Migraine: a chronic sympathetic nervous system disorder. *Headache*. 2004 Jan;44(1):53-64.

OBJECTIVES: To determine the degree of diagnostic and clinical similarity between chronic sympathetic nervous system disorders and migraine. Migraine is an episodic syndrome consisting of a variety of clinical features that result from dysfunction of the sympathetic nervous system. During headache-free periods, migraineurs have a reduction in sympathetic function compared to nonmigraineurs. Sympathetic nervous system dysfunction is

[22] Gupta S, Mehrotra S, Villalón CM, Perusquía M, Saxena PR, MaassenVanDenBrink A. Potential role of female sex hormones in the pathophysiology of migraine. *Pharmacol Ther*. 2007 Feb;113(2):321-40. Epub 2006 Oct 25.

[23] Fanciullacci M, Alessandri M, Bandini EB. The pathogenetic bases of hemicrania. *Ann Ital Med Int*. 1992 Jul-Sep;7(3 Suppl):41S-45S.

also the major feature of rare neurological disorders such as pure autonomic failure and multiple system atrophy. There are no known reports in the medical literature, however, comparing sympathetic nervous system function in individuals with migraine, pure autonomic failure, and multiple system atrophy. METHODS: A detailed review of the literature was performed to compare the results of a wide variety of diagnostic tests and clinical signs that have been described in these 3 heretofore unrelated disorders. RESULTS: The data indicate that migraine shares significant diagnostic and clinical features with both pure autonomic failure and multiple system atrophy, yet represents a distinct subtype of chronic sympathetic dysfunction. Migraine is most similar to pure autonomic failure in terms of reduced supine plasma norepinephrine levels, peripheral adrenergic receptor supersensitivity, and clinical symptomatology directly related to sympathetic nervous system dysfunction. The peripheral sympathetic nervous system dysfunction is much more severe in pure autonomic failure than in migraine. Migraine differs from both pure autonomic failure and multiple system atrophy in that migraineurs retain the ability, although suboptimal, to increase plasma norepinephrine levels following physiological stressors. CONCLUSIONS: The major finding of the present study is that migraine is a disorder of chronic sympathetic dysfunction, sharing many diagnostic and clinical characteristics with pure autonomic failure and multiple system atrophy. However, the sympathetic nervous system dysfunction in migraine differs from pure autonomic failure and multiple system atrophy in that occurs in an anatomically intact system. It is proposed that the sympathetic dysfunction in migraine relates to an imbalance of sympathetic co-transmitters. Specifically, it is suggested that a migraine attack is characterized by a relative depletion of sympathetic norepinephrine stores in conjunction with an increase in the release of other sympathetic cotransmitters such as dopamine, prostaglandins, adenosine triphosphate, and adenosine. An enhanced understanding of the sympathetic dysfunction in migraine may help to more effectively diagnose, prevent, and/or treat migraine and other types of headache.[24]

Migraine triggers

Some people find that their migraines are triggered by specific foods or lifestyle behaviours. Examples of such triggers include:

- certain foods - especially those containing tyramine, octopamine and synephrine or caffeine that cause vasospasm - such as chocolate, cheese, citrus fruits, coffee, tea
- alcohol e.g. red wine
- too much or too little sleep
- changes in hormone balance in women - such as periods, the pill, menopause and hormone replacement therapy
- emotional stress, or relaxation after a period of stress e.g. weekends or holidays
- irregular meals
- physical activity
- smoking

[24] Peroutka SJ. Migraine: a chronic sympathetic nervous system disorder. *Headache*. 2004 Jan;44(1):53-64.

- bright or flashing lights
- loud noise
- weather - high pressure conditions, changes in pressure, hot dry winds, change of season and exposure to sun and glare
- intense smells such as paint, fumes from cars or perfume
- Some food additives, such as nitrites, nitrates and monosodium glutamate (MSG)
- Overuse of painkillers or other conventional migraine medications

Michael's integrated theory of migraine

Despite all this detailed physiological detail, the cause of migraine remains curiously elusive. Is it possible to consolidate the various theories and observations related to migraine pain to make sense of migraine and provide a rationale for effective treatment?

If we are to make sense of migraine, we must surely begin from a different standpoint. This is that migraines are actually a restorative attempt by the body, mind and spirit (*vis medatrix naturae*) to achieve reparation of a substantially disordered internal economy. This notion has in fact recently been proposed by some migraine commentators -*"Similar to other internal organs, the brain has a pain system to signal tissue injury. The trigeminovascular system acts as a warning system, causing migraines to help "protect" the brain against insults such as ischemia, toxins, and intrinsic disease, just as angina pectoris "protects" the heart against ischemia."*[25]

If the pain and distress of migraine attacks are a means by which the body protects itself, it makes no sense in the long-term to use drugs to remove the symptoms of the disease. Instead we must look to put right the fundamental problems that have lead to the attack in the first place. The famous Chinese classic, the *Huang Di Nei Jing*, says that *"treating disease after it arises is like beginning to dig a well after one has become thirsty or like forging spears after war has already broken out."* Successful migraine treatment requires treatment *between* attacks to address the fundamental and individual disharmony of each patient. Whilst pain relief measures are of course justifiable, they are merely palliative and are most unlikely to demonstrate potential for eradicating migraines once and for all.

There is a marked tendency for those suffering migraine attacks to suffer from drowsiness and lethargy.[26] The sufferer seeks quiet and rest and generally feels cold. Understanding this key feature of migraine is the start point of determining effective treatment. It should be explained to migraine sufferers that migraines have a logic of their own and that the intense pain they suffer is actually a prayer for nutrition, rest and restoration. From the body/mind point of view, migraine is the solution rather than the problem since the migraine stops the patient in his/her tracks enforcing rest. And rest is something that migraine patients all too

[25] http://www.merckmedicus.com/pp/us/hcp/diseasemodules/migraine/pathophysiology_sub.jsp

[26] Lishman WA. *Organic Psychiatry: The Psychological Consequences of Cerebral Disorder*, 3rd edition, Blackwell Science Ltd., 1998,

often hardly ever allow themselves. Although it would be too simplistic to say there is a single migraine type, in my experience many migraine sufferers are perfectionists pushing themselves mercilessly ever onwards, only coming to a halt when migraines force them to their beds or rest.

Migraine patients frequently find that that their attacks occur during a let-down period such as weekends or holidays especially after intense activity.[27] In other words, the migraine occurs at precisely the time when they are trying to take it easy. It is worth speculating why this should be. I believe that many migraine subjects are addicted to their own biochemistry, in particular to the adrenergic chemicals produced by the SNS. These chemicals like adrenaline enable migraineurs to run an "internal overdraft facility" seriously depleting their vital reserves. Once the workaday routine is broken and the sufferer takes his/her foot of the adrenal accelerator, the deficit is revealed and the pathological processes discussed above that inexorably lead to migraine are enacted. In the final analysis, painkillers and triptans merely extend the overdraft facility but ultimately collapse must come because quite simply demand cannot exceed supply.

One of the most difficult tasks in helping many patients to become migraine free is to liberate them from their driven nature and habitual behaviour patterns. Many migraineurs need to be persuaded that eating regularly and leisurely and resting from time to time are a legitimate part of their lives. Sufferers frequently demonstrate the Peter Principle that (in a hierarchy) people "*are promoted to the level of their incompetence*". In other words, they are working or seeking to work beyond their capacity. But why should this be? The answer appears to be that they are unknowingly signed up to the Groucho Club - Groucho Marks famously quipping that he "*would never belong to any club that would have him as a member!*" Many migraineurs I have met suffer from a deep sense of inferiority which means they never give themselves credit for anything they do or have done. They are hard taskmasters only measuring themselves by what they perceive they have not yet done. Consequently they drive themselves to the point of exhaustion by fixing a punishing schedule and/or often working for someone (boss or partner) who sets such unrealistic goals. Their rather masochistic predisposition may frequently be associated with repressed anger and resentment allied to perfectionist tendencies which require compassion and time in the consulting room if real change is to be made.[28]

Somewhat surprisingly a feature of migraine, namely hypoglycaemia, is to a great extent ignored by researchers, seen at best as a mere trigger of the condition. One reason for this may be that the tests for hypoglycaemia currently employed measure only gross pathological changes whereas the migraines can be triggered by missing meals or eating high glycaemic foods. This mechanism is only now beginning to receive the attention it deserves from researchers looking

[27] Ibid.
28 Gerber WD, Schoenen J. Biobehavioral correlates in migraine: the role of hypersensitivity and information-processing dysfunction. *Cephalalgia.* 1998 Feb;18 Suppl 21:5-11.

at the role of insulin in provoking migraines.[29] Yet the connection seems rather obvious. The brain runs on glucose and oxygen and if glucose levels drop in someone who is already stressed to the point of exhaustion than brain function is likely to become disordered. The human brain is one of the most energy hungry organs in the body thereby increasing its vulnerability. The brain is only 2 percent of the body's weight, but accounts for more than 20 percent of total calories used making it easily the most energetic of our internal organs; the brain consumes energy at 10 times the rate of the rest of the body per gram of tissue.[30] The brain is at a considerable disadvantage in being subject to maximum gravitational force when we are upright and this can have significance in those (often women) who have low blood pressure. For this reason blood pressure should be checked on a regular basis in those who suffer from migraine. Faced with insufficient glucose and oxygen to supply the brain, the central nervous system will go into overdrive to try and maintain supply (see research paper 4 above re hypoxia). This can explain the phenomena of the onset of CSD, vasospasm and vasodilation that characterise migraine episodes which are often signalled by prodromal signs and symptoms such as mood changes, food cravings, drowsiness, thirst, and yawning several hours or even the day before the onset of a migraine. Failure to right the deficit leads inevitably to the leaking of polypeptide alarm chemicals that effectively bring the person concerned to a halt whatever the pressures of their schedule might be.

One is reminded of the comment of the American Physiomedical doctor WH Cook:

Regularity in periods of alternate labour and rest is characteristic of all vital action… The duration of an effort in any organ may have considerable range, but relaxation must come or the part will suffer from not receiving (in rest) a supply of nutrient equal to its waste…. The earliest departure of the tissues from under full control of the vital force will be the lack of ability to relax or contract… the balance of complementary action is lost….”[31]

Blood sugar levels can easily be disrupted by dieting or missing meals as well by eating too much after a relatively long period of going without food. Refined carbohydrates, sugar, sweets and chocolates can precipitate an insulin rush and a sugar crash. Diet needs to be tailored specifically to our levels of physical and mental activity. A high carbohydrate diet will sustain demanding exercise but may cause problems in someone sitting for hours on end at a computer terminal. Our increasingly virtual lifestyle is ill adapted to optimal performance given our genetic programming that has developed over countless millennia in very different circumstances (see table below). Our ancestral heritage gives us the capacity to produce an orchestra of flight and fight chemicals e.g. adrenaline, noradrenaline and cortisol. These go-go chemicals increase breathing and heart

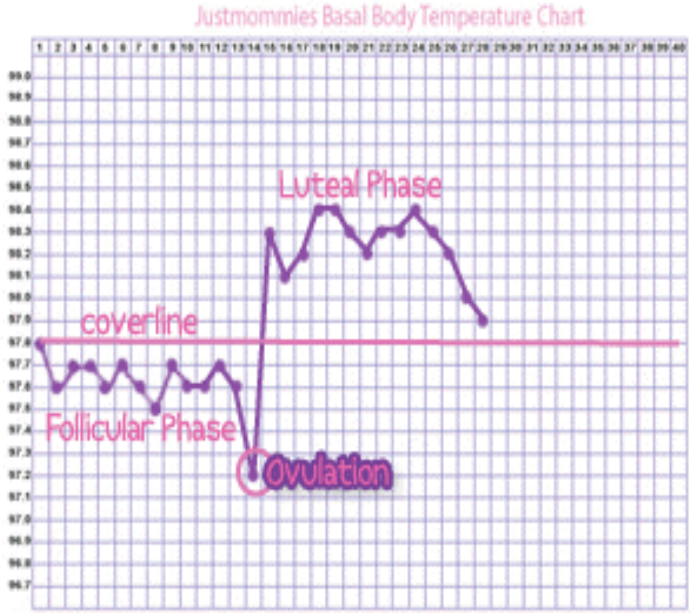
[29] Cavestro C, Rosatello A, Micca G, Ravotto M, Marino MP, Asteggiano G, Beghi E. Insulin metabolism is altered in migraineurs: a new pathogenic mechanism for migraine? *Headache.* 2007 Nov-Dec;47(10):1436-42.
[30] http://hypertextbook.com/facts/2001/JacquelineLing.shtml (accessed 2/11/08)
[31] Priest AW and Priest LR *Herbal Medication* LN Fowler and Co 1982

rates and raise blood pressure and pulse. Blood supply is diverted from non-essential organs such as the skin, intestines and kidneys and re-routed to the heart, brain and muscles. However, our 21st century lifestyle means all too often we produce them but we do not use them. Our bodies are flooded with the "fight or flight" chemicals but with no physical outlet we must wait for the reaction to subside. This is a major cause of the stress of modern life and fight and flight chemicals that are not burnt off by exercise can be potent migraine triggers either when we are inappropriately subject to high levels or when we switch off and our physiology crashes.

As discussed migraines affect many women and are often considered to be hormonally related – e.g. caused by oestrogen withdrawal.[32] However, here too it is worth exploring the possibility that many menstrual headaches are driven by failure of the body to provide adequate nutrition to the brain. In the second (luteal) phase of the menstrual cycle the body behaves as if it is pregnant under the influence of progesterone.

- Henry III was using sugar in 1264, but not until 1319 was sugar in more general use in Britain. It was sold at two shillings a pound (about £44 in today's money)

In a healthy woman the basal body temperature (BBT) rises significantly (see chart below) and this temperature rise has to be fuelled. In effect a woman at this phase of the cycle is providing nutrition to the brain and now to the uterus which represents a significant extra charge on the body's resources.



[32] MacGregor EA. Menstrual migraine. *Curr Opin Neurol*. 2008 Jun;21(3):309-15.

In the light of this it is surely not surprising that before the onset of menstruation many women have cravings for chocolate with its alluring blend of glucose and adrenergic chemicals, caffeine and theobromine or for other sweet foods. Treatment of menstrual migraines can be effectively tailored to the individual patient by examining BBT charts completed by the patient (see treatment section below).

Treatment of migraine (best done between attacks)

Use the pulse and tongue to help identify pattern of disharmony

1. Is the pulse weak, thready, slow and/or associated with pallor and low blood pressure and poor circulation? Is the tongue pale? Is the patient fatigued? Then tonify (support with trophorestoratives) and combine with warming digestive tonics and circulatory stimulants.
2. Is the pulse wiry (rises sharply/angularly against the palpating fingers like the string of a guitar, under the fingers)? Is it full or weak and thready and somewhat rapid? This is a type of pulse that demonstrates a continuing level of pathogenic stress. These patients generally have tight shoulder and neck muscles (e.g. *trapezius* and *sternocleidomastoid*) as well as contraction of face, and scalp muscles. Because of patients with this presentation may complain of a headache like a tight band round the head. Such patients will respond to relaxing nervine support. If the pulse is wiry-weak use relaxing nervines with tonics and nervines and circulatory stimulants – if the pulse is wiry-full increase the relaxing nervines and provide circulatory stimulants to equalise the circulation (i.e. to counter the possibility of hypoxia and pathological vasoconstriction and dilation).
3. Is the patient loud, hyperactive, red faced, irritable, impatient and living life in the fast lane spurred on by alcohol, nicotine and caffeine? This patient is likely to have a red tongue with a yellow coat and a full bounding pulse. In such cases use bitter “coolers” and relaxing nervines.
4. Is the patient emaciated, exhausted and dried out with a weak rapid pulse and a peeled red tongue? Patients with this presentation often complain of feeling hot or thirsty at night and may suffer night sweats. Long-term nourishment (trophorestoration) is necessary; it is by no means easy to deliver.
5. If the problem is menstrual migraines, are the follicular-phase temperature and the FSH reading too high? In this case use nervine herbs to calm the patient in this follicular phase and oestrogenic herbs to help the development of the follicles and bring down the FSH reading. Treat the luteal phase with a different strategy as outlined below.
6. In the treatment of menstrual migraines check the temperature in the luteal phase. Is it too low or does it fail to rise sharply within a day or so of ovulation? Alternatively the luteal phase temperature rises but falls before it should. In such cases check to see if the progesterone level too low? Is the tongue pale and pulse weak? Here use herbs to support the progesterone phase and warming circulatory, digestive and uterine tonics.

7. Treating pain is obviously something we need to address too. Use gentle pain relievers and in addition, equalise the circulation using digestive tonics to enable nourishment to be absorbed.

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Herbal formulations addressing the pattern outlines described above. The dosages are in grams and the mixtures are designed to be taken as a decoction.

1. *Treatment principle: Provide trophorestoration and warming circulatory stimulation*

Panax ginseng (red root in preference to the white) 5g (double boil in bain-marie)
Angelica sinensis (rad) 10
Avena sativa (semen) 10
Rosmarinus officinalis (herba) 5
Astragalus membranaceus (rad) 10
Apium graveolens (semen) 5
Gingko biloba (fol) 5
Cinnamon cassia (cortex) 5
Turnera diffusa (herba) 5
Stachys betonica (herba) 5
Thymus vulgaris (herba) 3
Glycyrriza glabra (rad) 3
Zingiberis officinalis (fresh root) 3

2a) Wiry, thready pulse, pale tongue. The patient is anxious, stressed and depressed.

Treatment principle: Relax and calm the patient, restore the nervous system and equalise the circulation.
Panax ginseng (Red) 5
Crataegus oxycantha (flos) 5 or Cinnamonum cassia (cortex) 5
Lavendula officinalis (flos)
Chrysanthemum morifolium (flos) 5
Citrus aurantium (flos) 5
Rosa rugosa (flos) – dried flower buds
Scutellaria laterifolia (herba) 5
Valeriana officinalis (radix) 5
Melissa officinalis (herba) 5
Stachys betonica (herba) 5
Passiflora incarnata (herba) 5
Avena sativa (semen) 10
Apium graveolens (semen) 3
Mentha arvensis (garden mint - herba) 3
Rosmarinus officinalis (herba) 3
Glycyrrhiza glabra (rad) 3

For pain give 5 drops of tincture of Anemone pulsatilla in aq. bds

2b) Wiry forceful pulse, red tongue tip and edges or red tongue body, severe throbbing headaches, patient anxious, irritable. Periods come early. Patient restless and hot at night.
Treatment principle: Relax and calm, equalise circulation and restore nervous equilibrium
Valeriana officinalis 5
Viburnum opulus (cortex) 5
Viscum album (herba) 5
Verbena officinalis (herba) 5
Passiflora incarnata 5
Primula vera (flos) 5
Matricara chamomilla (flos) 5
Melissa officinalis 5
Mentha arvensis 3
Stachys betonica 5
Angelica sinensis (rad) 5
Tanacetum parthenium (herba) 5

For pain give 5 drops of tincture of Anemone pulsatilla in aq. bds

3. The patient is loud, hyperactive, red faced, irritable, impatient. Full, bounding rapid pulse. Red tongue with yellow coat.
Treatment principle: Drain fire excess heat with cooling bitters, equalise the circulation
Tanacetum parthenium (herba) 5
Salix alba (cortex) 5
Gentiana lutea 5
Angelica sinensis 5
Stachys betonica 5
Chrysanthemum morifolium (flos) 5
Citrus reticulata (pericarpium) 5
Silybum marianum AKA Carduus marianus (semen) 5
Angelica archangelica (rad) 5
Crataegus oxycantha (fructus) 5
Viburnum opulus (herba) 5
Glycyrrhiza glabra 5

4. **Fundamental and severe draining of the body's vital reserves. Red peeled tongue and thready rapid pulse, dry mouth, tidal fevers, hot at night.**
Treatment principle: Provide trophorestoration to restore the body's vital reserves.
Seronoa serrulata (fructus) 10
Rehmannia glutinosa (radix preparata) 10
Chrysanthemum morifolium 5
Lycium chinensis (fructus) 10

Panax ginseng (white root) 5
Dioscorea villosa (radix) 10
Chamaelirium luteum 5
Althea officinalis (radix)10
Salvia officinalis (herba) 5
Avena sativa 10
Morus alba (fructus) 10

5a. **Menstrual migraines (follicular phase)**
Treatment principle: Nourish ovaries and vital reserves.
Chamaelirium luteum 10
Rehmannia glutinosa (preparata)
Angelica sinensis 10
Paeonia lactiflora (white peony root) 10
Seronoa serrulata 10
Cimicifuga racemosa 3
Mitchella repens 10
Dioscorea villosa 10
Lycium chinensis (fructus)

5b. Menstrual migraines (luteal phase)
Treatment principle: stimulate luteal phase, nourish the uterus
Ren Shen 6
Vitex agnus castus (semen) 10
Chamaelirium luteum 10
Turnera diffusa 10
Stachys betonica 10
Mitchella repens 10
Avena sativa 10
Salvia officinalis 5
Trigonella foenum-graecum (semen) 5
Cuscuta chinensis 10 (Dodder seeds) 10
Rehmannia glutinosa (preparata) 5

5c. Menstrual headaches associated with PMS and dysmenorrhea
Treatment principle: regulate menstruation and ease headache.
Leonurus cardiaca (herba) 10
Tanacetum parthenium 5
Carthamnus tinctoria (flos) 10
Angelica sinensis 10
Corydalis yanhusuo (rhizoma) 5 [33]
Rosa rugosa (flos) 5
Paeonia lactiflora 10
Thymus 5
Viburnum opulus 10

[33] This is a Chinese remedy; the European version is C. bulbosa (contains bulbocapine – hypnotic and spasmolytic).

Curcuma longa 5
Caulophyllum thalictroides 5
Calendula officinalis (flos) 10
Verbena officinalis 5

5d.) **Headaches after periods. Sallow complexion, pale tongue, thready pulse** *Treatment principle: Nourish blood and vitality, equalize circulation to stop headaches.*

Astragalus memb. 15
Panax ginseng 5
Gingko biloba 5
Angelica sinensis 10
Carthamnus tinctorius 10
Cinnamonum cassia 5
Angelica archangelica (herba et radix)10
Stachys betonica 10
Dioscorea villosa 10
Thymus vulgaris 5
Rosmarinus officinalis 5
Salvia officinalis 5
Gycyrrhiza glabra 3

6. Pain relief:

Herbs such as: Anenome puls., Matricaria, Filipendula, Salix alb, Chrysanthethum morifolium, Verbena, Salvia, Tilea, Thymus, Salvia, Corydalis yanhu suo (rhizoma), Escholzia, Gelsemium, Lavender EO.

Some further relevant research papers etc.

Shrivastava R, Pechadre JC, John GW. Tanacetum parthenium and Salix alba (Mig-RL) combination in migraine prophylaxis: a prospective, open-label study. *Clin Drug Investig*. 2006;26(5):287-96.

BACKGROUND: Tanacetum parthenium (feverfew) has been used traditionally to treat migraine, and although its mechanism of action is not fully understood, serotonin 5-HT receptor blocking effects have been suggested. T. parthenium and Salix alba (white willow) either alone or in combination (Mig-RL) were recently shown to inhibit binding to 5-HT(2A/2C) receptors; T. parthenium failed to recognise 5-HT(1D) receptors, whereas S. alba or the combination did. It was hypothesised that S. alba in combination with T. parthenium may provide superior migraine prophylactic activity compared with T. parthenium alone. METHODS: A prospective, open-label study was performed in 12 patients diagnosed with migraine without aura. Twelve weeks' treatment with T. parthenium 300 mg plus S. alba 300 mg (Mig-RL) twice daily was administered to determine the effects of therapy on migraine attack frequency (primary efficacy criterion), intensity and duration (secondary efficacy criteria), and quality of life, together with tolerability for patients. RESULTS: Attack frequency was reduced by 57.2% at 6 weeks ($p < 0.029$) and by 61.7% at 12 weeks ($p < 0.025$) in nine of ten patients,

with 70% patients having a reduction of at least 50%. Attack intensity was reduced by 38.7% at 6 weeks ($p < 0.005$) and by 62.6% at 12 weeks ($p < 0.004$) in ten of ten patients, with 70% of patients having a reduction of at least 50%. Attack duration decreased by 67.2% at 6 weeks ($p < 0.001$) and by 76.2% at 12 weeks ($p < 0.001$) in ten of ten patients. Two patients were excluded for reasons unrelated to treatment. Self-assessed general health, physical performance, memory and anxiety also improved by the end of the study. Mig-RL treatment was well tolerated and no adverse events occurred. CONCLUSION: The remarkable efficacy of Mig-RL in not only reducing the frequency of migraine attacks but also their pain intensity and duration in this trial warrants further investigation of this therapy in a double-blind, randomised, placebo-controlled investigation involving a larger patient population.

Reay JL, Kennedy DO, Scholey AB. Effects of Panax ginseng, consumed with and without glucose, on blood glucose levels and cognitive performance during sustained 'mentally demanding' tasks.
J Psychopharmacol. 2006 Nov;20(6):771-81. Epub 2006 Jan 9.

Single doses of the traditional herbal treatment Panax ginseng have recently been shown to lower blood glucose levels and elicit cognitive improvements in healthy, overnight-fasted volunteers. The specific mechanisms responsible for these effects are not known. However, cognitive improvements may be related to the glycaemic properties of Panax ginseng. Using a double-blind, placebo-controlled, balanced-crossover design, 27 healthy young adults completed a 10 minute "cognitive demand" test battery at baseline. They then consumed capsules containing either ginseng (extract G115) or a placebo and 30 minutes later a drink containing glucose or placebo. A further 30 minutes later (i.e. 60 minutes post-baseline/capsules) they completed the "cognitive demand" battery six times in immediate succession. Depending on the condition to which the participant was allocated on that particular day, the combination of capsules/drink treatments corresponded to a dose of: 0mg G115/0 mg glucose (placebo); 200mg G115/0 mg glucose (ginseng); 0 mg G115/25 g glucose (glucose) or 200 mg G115/25 g glucose (ginseng/glucose combination). The 10 minute "cognitive demand" battery comprised a Serial Threes subtraction task (2 min); a Serial Sevens subtraction task (2 min); a Rapid Visual Information Processing task (5 min); and a "mental fatigue" visual analogue scale. Blood glucose levels were measured prior to the day's treatment, and before and after the post-dose completions of the battery. The results showed that both Panax ginseng and glucose enhanced performance of a mental arithmetic task and ameliorated the increase in subjective feelings of mental fatigue experienced by participants during the later stages of the sustained, cognitively demanding task performance. Accuracy of performing the Rapid Visual Information Processing task (RVIP) was also improved following the glucose load. There was no evidence of a synergistic relationship between Panax ginseng and exogenous glucose ingestion on any cognitive outcome measure. Panax ginseng caused a reduction in blood glucose levels 1 hour following consumption when ingested without glucose. These results confirm that Panax ginseng may possess glucoregulatory properties and can enhance cognitive performance.

From issue 2061 of New Scientist magazine, 21 December 1996, page 18
Friday, 14 April, 2000, 09:38 GMT 10:38 UK
Herbal remedies 'boost brain power'
A combination of two ancient herbal remedies can dramatically boost brain power and may have applications in medicine, say scientists.
Researchers showed that ginkgo biloba can improve the power of concentration, while ginseng sharpens up the memory.
The effect was even more powerful if the two herbs were taken together.
The researchers believe the instant hit may help students to improve exam performance, and businessmen clinch a crucial deal.
They suggest the herbs may also be useful in treating neurological disorders - ginkgo is already used in some countries to treat Alzheimer's disease.

These results suggest that such extracts may have many other medical applications such as helping people recover from local anaesthetics

Researcher Dr Andrew Scholey, from the University of Northumbria said: "These results suggest that such extracts may have many other medical applications such as helping people recover from local anaesthetics."
Dr Scholey said researchers had long looked for a drug that improves both memory and concentration.
"Normally when you speed people up you lose a bit of accuracy, or if they are more accurate they take longer to respond.
"These two herbs added together synergistically in a remarkable way."
Both herbal extracts have been used for thousands of years in China.
They are supposed to boost energy and performance when taken over a long period of time.
However, Dr Scholey's team discovered ginkgo improved attentiveness after just one dose.
Volunteers displayed much faster reaction times in tests requiring concentration.
Dr Scholey said: "Subjects were able to sustain their concentration for longer. Normally when people have to concentrate over an extended period of time, their reaction time begins to slow - ginkgo seemed to stop that slowing and one dose actually speeded them up."
The research also showed that ginseng rapidly boosted memory.
"With every dose there was improvement in the subjects' ability to store, hold and retrieve information, and one dose caused a particularly dramatic improvement."
The most significant impact of all was when volunteers took a preparation of 60% ginseng and 40% ginkgo.
They were then asked to take part in a simple maths test, repeatedly subtracting the number seven or three from a series of figures.
Dr Scholey said: "People were performing serial sevens at the same rate as serial threes.
"This is a remarkable finding. What seems to be happening is that it is improving the available mental energy."
The most effective doses were 400mg of ginseng, 360mg of ginkgo, and 960mg of the two combined.
The researchers presented their results at the British Psychological Society's annual conference in Winchester.
The study was funded by Pharmaton, a company that produces ginkgo and ginseng preparations, but Dr Scholey insisted the research was scrupulously independent.

Kennedy DO, Scholey AB. The psychopharmacology of European herbs with cognition-enhancing properties. *Curr Pharm Des*. 2006;12(35):4613-23.

Extensive research suggests that a number of plant-derived chemicals and traditional Oriental herbal remedies possess cognition-enhancing properties. Widely used current treatments for dementia include extracts of Ginkgo biloba and several alkaloidal, and therefore toxic, plant-derived cholinergic agents. Several non-toxic, European herbal species have pan-cultural traditions as treatments for cognitive deficits, including those associated with ageing. To date they have not received research interest commensurate with their potential utility. Particularly promising candidate species include sage (Salvia lavandulaefolia/officinalis), Lemon balm (Melissa officinalis) and rosemary (Rosmarinus officinalis). In the case of sage, extracts possess anti-oxidant, estrogenic, and anti-inflammatory properties, and specifically inhibit butyryl- and acetyl-cholinesterase. Acute administration has also been found to reliably improve mnemonic performance in healthy young and elderly cohorts, whilst a chronic regime has been shown to attenuate cognitive declines in sufferers from Alzheimer's disease. In the case of Melissa officinalis, extracts have, most notably, been shown to bind directly to both nicotinic and muscarinic receptors in human brain tissue. This property has been shown to vary with extraction method and strain. Robust anxiolytic effects have also been demonstrated following acute administration to healthy humans, with mnemonic enhancement restricted to an extract with high cholinergic binding properties. Chronic regimes of aromatherapy and essential oil respectively have also been shown to reduce agitation and attenuate cognitive declines in sufferers from dementia. Given the side effect profile of prescribed cholinesterase inhibitors, and a current lack of a well tolerated nicotinic receptor agonist, these herbal treatments may well provide effective and well-tolerated treatments for dementia, either alone, in combination, or as an adjunct to conventional treatments.