This symposium provided a review of published reports and presentations of novel data, which together served to define and explicate an understanding of the alcoholic Wernicke-Korsakoff Syndrome (WKS) from the clinical and basic science perspectives. The symposium's five presentations covered neuropathology, epidemiology, neural and genetic mechanisms, neuropsychological and neuroradiological signs of Wernicke's encephalopathy (WE) and Korsakoff's syndrome (KS), and therapeutic approaches to reduce or reverse the potentially devastating and life threatening condition of WKS. The essence of each of the five talks is presented here, and each contributor provided references from the literature to direct scientists and clinicians interested in WKS to primary research sources.

1. Brain Damage Caused by Thiamin Deficiency – The Australian Experience
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The Wernicke-Korsakoff syndrome (WKS) is caused by thiamine deficiency but is seen commonly in alcoholic cases (Harper, 2006). It is consistently reported in the literature even though it is easily treated or even prevented by thiamine. The focus of our research has been the pathological changes in the brain with long-term abuse of alcohol. Using human brain tissues from the New South Wales Tissue Resource Center (TRC) (Harper et al., 2003a; Harper et al., 2003b) we have tried to identify the most important factors that cause alcohol-related brain damage. These include direct toxic effects of alcohol, thiamine (vitamin B1) deficiency (WKS) and hepatic encephalopathy. These toxic, metabolic and nutritional factors interact in a complex fashion and may have similar pathogenetic mechanisms and molecular pathways (Harper and Matsumoto, 2005). Carefully documented alcoholic cases were studied using quantitative morphometry and immunohistochemistry (Harper, 1998). Regional volumes, neuronal counts and densities were calculated and specific populations of neurons were studied (e.g., serotonergic, cholinergic and adrenergic systems (Halliday and Baker, 1996; Halliday et al., 1995; Halliday et al., 1994). In alcoholic subjects who have no other medical complications (cirrhosis or WKS) the white matter is a primary target for damage (Harper and Kril, 1986), whereas only select populations of neurons are susceptible (superior frontal cortex) (Harper, 1998). These findings correlate with neuropsychological and neuroradiological data (Oscar-Berman and Hutner, 1993; Pfefferbaum et al., 1997). In cases with the WKS there is more widespread pathological damage in cortical, subcortical and cerebellar regions (Harper and Kril, 1990). The anatomical substrate for the severe amnesic syndrome seen clinically in the Korsakoff syndrome was identified by Harding and his colleagues using TRC cases – the critical site of damage appears to be the anterior nucleus of the thalamus (Harding et al., 2000).

Autopsy studies in the 1980s indicated that WKS was more common in Australia than any other country in the world (Harper et al., 1995; Harper et al., 1989; Harper, 1983a; Harper, 1983b). Nutritional studies also indicated that a significant proportion of the Australian population was thiamine depleted (Wood, 1985). In 1991 a public health measure of mandatory enrichment of bread flour with thiamine in all States of Australia
was introduced to address these problems. To determine the effectiveness of this program another prevalence study was done in forensic autopsy cases in Sydney in 1997 (Harper et al., 1998). Twenty-five cases of WKS were identified in the 2212 sequential autopsies studied. This is a prevalence rate of 1.1%, which is significantly less (P<0.0001) than a previous similar Australian study (4.7%) (Harper, 1983a; Harper et al., 1998). Factors that might have had impacts on this reduction include a change in per capita alcohol consumption (Jonas et al., 2000; Wodak, 1986), an increase in numbers of alcohol treatment centers, oral thiamine therapy and an improvement in health generally. However, we believe that thiamine supplementation of foods has played a part and should be seen as a useful and cost effective public health measure, particularly for people with excessive alcohol intakes.

References
2. Glutamate-Mediated Excitotoxicity in Wernicke's Encephalopathy

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Wernicke-Korsakoff syndrome (WKS) is a neuropsychiatric disorder characterized by changes in behaviour that include a striking memory loss, oculomotor disturbances and ataxia, in which the underlying cause is thiamine deficiency (TD). Wernicke’s encephalopathy (WE), the neurological component of WKS, is identified neuropathologically by the presence of focal neuronal damage in areas that include the thalamus, inferior colliculus, mammillary bodies, and cerebral cortex. Considerable evidence suggests a key role of glutamate in the pathophysiology of TD. Early studies include reports of glutamate levels being reduced in whole brain of TD animals (Gubler et al., 1974), consistent with earlier reports of a decrease in the conversion of [¹⁴C]glucose to glutamate in TD rats (Gaitonde et al., 1975) and reduced Ca²⁺-dependent release of glutamate in hippocampal slices from symptomatic animals (Lê et al., 1991). In addition, Armstrong-James and co-workers (1988) reported a similarity in the appearance and development of the central thalamic lesion in TD to that observed following intrathalamic administration of excitatory amino acids, and treatment with the noncompetitive NMDA receptor antagonist MK-801 was shown to lead to a reduction in the extent of neuronal damage in TD rats (Langlais and Mair, 1990).

In 1993, we provided the first direct evidence that histological vulnerability in the thalamus of TD rats was associated with focal increases in extracellular glutamate concentration (Hazell et al., 1993). More recently, it was demonstrated that the thalamus exhibits a dramatic loss of the astrocytic glutamate transporters EAAT1 and EAAT2 (Hazell et al., 2001), which likely plays a major role in the elevation of interstitial glutamate levels observed in this brain region, with antioxidant treatment using N-acetylcysteine preventing loss of EAAT2 levels and neuronal cell loss in this brain region. Downregulation of both EAAT1 and EAAT2 in association with neuronal loss was also observed in the frontal cortex of patients with neuropathologically-confirmed
WE. In astrocyte cultures, loss of EAAT1 transporter levels due to TD can be prevented by treatment with the protein kinase C inhibitor H7 (Hazell et al., 2003), suggesting that phosphorylation may be involved in EAAT downregulation.

More recently, genomic analysis of the thalamus in TD identified a 68-fold increase in expression of heat shock protein 27 (Hsp27) (Vemuganti et al., 2006) that translated into a 19-fold elevation in Hsp27 protein. Cultured astrocytes showed an increase in Hsp27 levels when exposed to TD conditions concomitant with a loss of EAAT1 content, indicating that increased Hsp27 levels are also correlated with loss of glutamate transporters under these conditions. Knockdown of Hsp27 with RNA interference in these cells led to a loss of both Hsp27 and EAAT1 but not beta-actin, suggesting maintenance of transporter levels is at least partly dependent on the levels of this chaperone protein.

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**References**


3. Biochemistry of Thiamine Transport and Genetic Susceptibility to Wernicke Korsakoff Syndrome

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The Wernicke Korsakoff Syndrome (WKS) is a neurodegenerative disorder caused by a combination of alcohol misuse and deficiency of vitamin B1 (thiamine). Thiamine plays an essential role in normal cellular functions via its involvement as a co-factor in the glucose/energy metabolism (Todd and Butterworth, 1999). In humans, thiamine cannot be synthesized and must therefore be obtained from exogenous sources, through absorption in the intestine (Singleton and Martin, 2001).

The cellular transport of thiamine is mediated by specific carriers, recently identified and biochemically characterised: the Thiamine Transporter-1 and Transporter-2, the products of the SLC19A2 and SLC19A3 genes, respectively (Diaz et al., 1999; Ganapathy et al., 2004). Gene expression studies have shown that the thiamine transporters are well expressed in several tissues, such the intestine, placenta, kidneys and brain. A genetic susceptibility in the pathogenesis of Wernicke Korsakoff Syndrome (WKS) has been hypothesised and the thiamine transporters are good candidate genes. We report the screening of the high affinity Thiamine Transporter gene, SLC19A2 on chromosome 1q23.2-q23.3, and of the low affinity thiamine transporter gene, SLC19A3 on chromosome 2q36.3. We have carried out semi-automated direct genomic PCR sequencing in 30 alcoholics patients affected by WKS and in 30 super-normal controls, and identified several genetic variants in SLC19A2 (exon 6, 3’ UTR region) (Guerrini et al., 2005) and SLC19A3 (promoter and intron 1). These genetic variants are not described as common polymorphism in published databases.

Although a genetic component in the pathogenesis of WKS has been postulated since the late seventies, very few genetic studies have been carried out. In this research we attempted to evaluate the potential role of genomic variants of the high and low affinity transporter in the pathophysiology of WKS. Inferring function and abnormal function of these variants from the position they occupy in the gene is complex, and the literature encourages caution in dismissing or implicating an effect from any base pair changes in any given gene. The small sample size precludes any firm inferences about the possible functional significance of these genetic variants in WKS. The fact that a deletion and a base pair substitution only were found in cases warrants further investigation in larger samples. Functional studies are also needed in order to evaluate the impact of these genetic variants on the protein expression pattern. This project is still in progress; we collected 80 WKS patients, 550 non-WKS alcoholics and 600 healthy controls, and we are currently analysing Single Nucleotide Polymorphisms in several thiamine related genes.
4. Neuroradiological and Neuropsychological Signs of WKS

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Wernicke's Encephalopathy (WE) is caused by thiamine deficiency, most commonly occurring with chronic alcoholism (Harper et al., 1995; Martin et al., 2003; Thomson et al., 2002b). WE is said to present with the classical neurological triad of ophthalmoplegia, ataxia of gait, and mental confusion, but the complete triad of signs seldom occurs (Caine et al., 1997), and is associated with lesions in thalamus, mammillary nuclei, and inferior colliculi (Victor et al., 1971; Victor et al., 1989). Parenteral thiamine treatment given in the early symptomatic stages largely reverses the neurological signs (Caine et al., 1997; Thomson et al., 2002a; Victor et al., 1971; Victor et al., 1989), but undertreated cases may show the enduring amnesia and ataxia defining the chronic sequelae of Korsakoff's Syndrome (KS) (Butters and Cermak, 1980; Kopelman, 1995; Talland, 1965; Victor et al., 1959).

Neuroradiological signs of acute WE are marked by signal hyperintensity in thalamus, periventricular gray matter, inferior colliculus, and occasionally in cerebellum (Charness, 1993). These observations are consistent with postmortem reports (e.g., Baker et al., 1999; Harper and Kril, 1988; Harper and Kril, 1990; Kril et al., 1997; Torvik et al., 1982; Torvik et al., 1986), and partial lesion resolution with thiamine treatment. Given the wide variety of precipitating conditions, devastating morbidities, and likelihood of premature mortality (c.f., Harper and Butterworth, 1997; Harper et al., 1995; Harper et al., 1998), it remains clinically relevant to be able to identify the neuroradiological signature of thiamine deficiency in an animal model of WE with a known etiology and treatment and to track the brain lesion profile and its resolution with treatment-associated recovery.

Our studies of alcoholics with KS, alcoholics "uncomplicated" by KS, and healthy controls quantify regional brain volumes with magnetic resonance imaging (MRI). Contemporaneously, neuropsychological tests assess multiple functional
domains, including executive functions, declarative and procedural memory, visuospatial abilities, and static balance. To date, the MRI studies have demonstrated graded regional brain volume shrinkage or compromised tissue quality, where deficits of uncomplicated alcoholics were significant but less severe than those of KS in the mammillary bodies (Sullivan et al., 1999), thalamus (Sullivan, 2003), pons (Sullivan and Pfefferbaum, 2001), hippocampus (Sullivan and Marsh, 2003), cerebellar hemispheres and anterior superior vermis (Sullivan et al., 2000). Because of the edematous nature of acute WE lesions, MRI methods sensitive to fluid presence in tissue have revealed bilaterally distributed hyperintensities in medial thalamus, mammillary bodies, periaqueductal gray matter (e.g., nonalcoholic WE: Chu et al., 2002; Doraiswamy et al., 1994; Unlu et al., 2005; Zhong et al., 2005) (alcoholic WE: Schroth et al., 1991). As the edema and inflammation resolve, the mammillary bodies become atrophic (Charness and DeLaPaz, 1987), a progression detectable with in vivo imaging.

As reported by a number of laboratories, we have found profound impairment in KS in declarative memory for current and remote events, visual figure-ground perception, and balance with sparing of general intelligence, short-term memory, and visuoperceptual implicit learning (Fama et al., 2004; Fama et al., 2006). Contrary to traditional belief (c.f., Squire et al., 1990), we observed that KS patients had hippocampal volume deficits equivalent to those in patients with Alzheimer's disease, which is characterized by hippocampal volume deficits (Sullivan and Marsh, 2003). Further, declarative memory performance by KS patients related to hippocampal volume deficits (Sullivan and Marsh, 2003), whereas historical event naming and sequencing related to frontoparietal white matter volumes (Fama et al., 2004).

Whether thiamine deficiency is a necessary or sufficient cause of alcoholism-related brain volume and neuropsychological deficits remains a question in humans. Animal models of the alcoholism-nutritional interaction suggest compounded effects on thalamic volume recovery and global functioning but a primary thiamine deficiency effect on the thalamus, mammillary nuclei, inferior colliculi, lateral and fourth ventricles, and hippocampus (Zimitat et al., 1990). Recently, we were able to detect the pattern of pyrithiamine-induced lesions in alcohol-preferring rats that is characteristic of human KS and track the longitudinal progression of the pathology using in vivo MR imaging and spectroscopy. We observed image signal hyperintensities, indicative of boggy tissue, in the thalamus, mammillary bodies, and inferior colliculi that were greatest in the pyrithiamine-treated rats with a history of alcohol exposure (Pfefferbaum et al., 2006). Although the inferior colliculus lesions resolved with time and thiamine repletion, the thalamus lesions showed only partial recovery, both structurally and with respect to neuronal integrity (i.e., partial recovery occurred in N-acetylaspartate, measured with MR spectroscopy) and the mammillary bodies showed no recovery. Postmortem analysis on the corpus callosum of these rats revealed a compounded effect of alcohol and pyrithiamine treatment on myelin thinning and over-representation of small diameter fibers (He et al., 2007).

The combined alcohol dependency and nutritional deficiency, especially of Vitamin B1, are candidate substrates for the enduring brain structural volume and tissue quality abnormalities and cognitive and motor impairments defining alcoholic WE and KS.
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5. Clinical Aspects of Wernicke-Korsakoff Syndrome: From Diagnosis to Treatment and Prevention

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The successful treatment of Wernicke’s encephalopathy (WE) depends upon providing the depleted brain cells with adequate levels of thiamine (vitamin B1) before any permanent brain damage, Korsakoff’s psychosis (KP) has occurred (Cook et al., 1998). Autopsy studies have shown that the diagnosis of WE is missed in approximately 80% of patients and that the classic triad of signs is an unreliable diagnostic indicator. 1.5% of autopsy subjects in general hospitals around the world have lesions of WE and 12.5% of alcoholic subjects are similarly affected. In the Western World 90% of cases of WE are associated with alcohol misuse (Harper et al., 1995; Thomson et al., 2002). It is important to identify patients at risk of developing WE so that they can be given prophylactic thiamine. We have reviewed 15 clinical studies, performed during the last 125 years, in which the diagnosis of WE has been confirmed at autopsy. A number of prodromal signs and symptoms of thiamine depletion have been identified, such as anorexia, weight loss, recurrent vomiting, fatigue/weakness etc. (Thomson and Marshall, 2006a). Using these criteria patients should be given 250mg of thiamine hydrochloride IM prophylactically for 3 to 5 days. Criteria have also been identified for making a presumptive or definite diagnosis of WE (Caine et al., 1997). Some patients require 1.0 gm of thiamine a day, and lower doses have not been reliably effective at preventing KP. Therefore, patients should be given 500 mg of thiamine IV in saline over a period of 30 minutes three times daily for 2 days, followed by 250 mg IV daily for a further 5 days (Thomson and Marshall, 2006b).
Thiamine therapy is associated with a small risk of anaphylaxis/anaphylactoid reactions and giving it by slow IV infusion reduces the risk. It is also important to correct any other nutrient deficiencies required for normal brain function especially Mg++ levels.

The recommendations for thiamine therapy are the result of clinical experience and not determined by dose - ranging placebo-controlled trials. The long-term outcome of treatment will depend upon prompt and adequate thiamine replacement but may be limited by the degree of neurotoxicity secondary to the metabolism of excessive alcohol intake.

References