The famous monologue from Shakespeare’s *As You Like It*, from which the title of this contribution is taken, likens the world to a stage and life to a play. The seven stages of man’s life are vividly evoked and have resonance today, even as we view the effects of alcohol consumption on the individual across the life course. First we see the infant ‘mewling and puking in his nurse’s arms’, then the child ‘creeping like snail unwillingly to school’. The lover (or modern day adolescent) ‘sighing like a furnace’ gives way to the soldier (or young adult) ‘sudden and quick in quarrel’. The ‘justice’ (modern day adult) is ‘full of wise saws and modern instances’ and ‘so plays his part’. With the arrival of the sixth age, we see the older man shrinking in stature. Finally the dying man is again like a child: ‘sans teeth, sans eyes, sans taste, sans everything’.

Alcohol-related brain damage is a heterogeneous condition. There is no single causal mechanism. Alcohol and its metabolite acetaldehyde have a direct neurotoxic effect on the brain. Repeated episodes of intoxication and withdrawal, dietary neglect and thiamine and other vitamin deficiencies, traumatic brain injury, cerebrovascular events and alcoholic liver disease also contribute to impairment in brain structure and function. These direct and indirect effects of alcohol interact in the individual, such that no two people drinking the same amount of alcohol develop the same patterns of damage. Individual susceptibility is influenced by prenatal exposure to alcohol, age, gender, genetic predisposition (Guerrini *et al.*, in this issue), general health, social inequalities and other metabolic influences.

Alcohol-related brain damage (ARBD) manifests itself in different ways across the lifespan. In the developing fetal brain, neuronal and glial cells divide rapidly to the extent that they total ∼2 billion in number by the time of birth. Alcohol exerts its neurotoxic effects directly on these neurons causing apoptosis (cell death), thus alcohol misuse in pregnancy has the potential to cause severe fetal brain damage (Guerrini *et al.*, 2007). Babies born with Fetal Alcohol Spectrum Disorders will have life-long behavioural, social and cognitive impairments (Guerrini *et al.*, in this issue). The (still developing) adolescent brain is vulnerable to the effects of alcohol, and particularly to the pattern of binge drinking typical of this age group. Binge drinking has an impact on learning skills and problem solving (Crews and Nixon, in this issue). Abstinence facilitates neuro-regeneration and an improvement in cognitive abilities. The extent and the severity of brain damage are also related to other co-factors such as gender and nutrition. The combination of these co-factors with alcohol misuse potentially has a cumulative effect on the severity of brain damage and an impact on the recovery process.

The cumulative effects of alcohol consumption have the potential to influence human behaviour, thereby predisposing adolescents to future damage. Although abstinence can lead to improvements in neuropsychological functioning and neuroimaging, individuals are often left with subtle deficits that have an impact on their quality of life. Heavy drinking adolescents are not only limiting their experience of the world but are also interfering with the normal brain maturation processes and this can lead to life-long problems in sustaining relationships, employment and personal well-being.

The pioneering work of Clive Harper has demonstrated that we often fail to make the diagnosis of Wernicke’s encephalopathy (WE) clinically and many patients who survive are to be found in nursing homes around the world where the true cause of their brain damage remains unappreciated and untreated. The pathogenesis of WE is now better understood (Thomson and Marshall, 2006), and the early signs and symptoms of thiamine deficiency have been identified together with predisposing factors that put patients at particular risk (Thomson and Marshall, 2006). Despite this, individuals who misuse alcohol continue to ‘fall through the net’. Wernicke could be forgiven for thinking that, 127 years after he published his series of patients in 1881, not much has changed! (Thomson *et al.*, 2008).

The role of MRI as a diagnostic tool in WE, confirming clinical suspicion, is highlighted in Sullivan and Pfefferbaum’s paper (in this issue). They also draw attention to the value of longitudinal MRI examinations, before and after treatment, documenting progress, further damage, and the potential for lingering ‘neuroradiological traces of WE’ to interact with other neurodegenerative conditions and the ageing brain.

Although the neuropathological consequences of thiamine deficiency have been well characterized, the mechanisms leading to these selective histological lesions have not been fully identified. Hazell and Butterworth (in this issue) review the relative and inter-related roles of oxidative stress, glutamate-mediated excitotoxicity and inflammation in thiamine deficiency. Although it is still unclear how these processes lead to focal neuronal loss, the study of thiamine deficiency may provide new insights into the pathophysiology of Alzheimer’s disease, Parkinson’s disease and other disease conditions in which these processes occur.

Proteomics technology allows us to understand the mechanisms of alcohol-related brain damage at the level of protein expression. Matsumoto (in this issue) demonstrates that various ‘alcohol-sensitive’ brain regions react differently to chronic alcohol ingestion at the level of protein expression. He raises the possibility that thiamine deficiency may be more widespread...
than generally believed, resulting in alteration of the protein expression profiles in these regions even before the clinical onset of WKS symptoms.

There remains the unresolved problem of how much parenteral thiamine is required to treat WE successfully. Some countries continue to treat suspected Wernicke episodes with only 100–200 mg of parenteral thiamine, even though Victor et al. (1989) and Wood et al. (1986) were of the view that between 56% and 86% of patients treated in this way were at risk of developing the Korsakoff syndrome. The upper limit of the dose required relies on individual case reports of patients who only responded to treatment when they were given >1.0 g of parenteral thiamine in 24 h. There have been no double-blind controlled trials testing dose requirements, and it is unlikely that these will be carried out in the future because of ethical constraints. Even though some patients will receive more thiamine than they might require, it will be difficult to refine the dose further. Until we have additional information, it would seem better to give too much thiamine to some patients than to give too little, too late, to others.

It is important to remember that WE patients may be refractory to treatment due to magnesium deficiency: magnesium acts as a co-factor for many thiamine dependent enzymes (Thomson and Marshall, 2006).

There are also important differences in the treatment of WE in different countries. For example, the only parenteral high potency B-complex vitamin therapy available in the UK is Pabrinex. This contains riboflavin and pyridoxine, which theoretically may limit the accumulation of glutamate in the presence of thiamine deficiency (Thomson, 2000) and also nicotinamide, which may correct unsuspected nicotinic acid deficiency and may help prevent the development of alcoholic pellagra encephalopathy (Thomson and Marshall, 2006). Interesting recent work by Green et al. (2008) in mice found that nicotinamide protected the animals from memory loss associated with a condition similar to Alzheimer’s disease.

For the remainder of individuals who develop the Korsakoff syndrome, much work remains to be done to define the optimum treatment they require to facilitate improvement (paper by Kopelman et al., in this issue).

In this Special Issue we bring together a series of papers ranging from the adverse effects of alcohol misuse at the cellular level to the widespread effects of alcohol on society and the associated public health issues. There have been some very interesting biochemical findings that help us understand the combined effects of thiamine deficiency and ethanol toxicity as well as the consequences of binge drinking (Ward et al., in this issue). We have seen the damage to the brain demonstrated by the latest scanning techniques and the ‘gold standard’ method of diagnosis—autopsy (Harper, in this issue). How these factors operate during the ‘Seven Ages of Man–Woman’ will be difficult and complicated to explain. However, it is obvious that earlier interventions can attenuate or (even better) prevent the development of alcohol-related brain damage. The utility of biomarkers in the early detection of alcohol-related thiamine deficiency is discussed by Mancinelli and Ceccanti (in this issue).

For many years, it has been suspected that some drinkers have a genetic predisposition to the development of WE. Recent work suggests that genetic abnormalities in thiamine metabolism and transport may play a part in what is likely to be a multiple genetic abnormality which puts these patients at risk.

In this special issue we have presented the latest views on alcohol-related brain damage that document the advances that have been made and give us considerable optimism for future understanding and prevention of this condition. The public should be given information about how alcohol affects the brain, so that they can make up their mind about how to drink. What is required is the political will and medical determination to educate all members of the medical and allied professions who are likely to be responsible for individuals with alcohol-related brain damage. Much has been achieved over the last 40 years in highlighting and treating the effects of alcohol on the liver. In many ways, alcohol-related brain damage is more fundamental and its effects on society more profound. It is time that equal efforts were made to protect what makes us who we are, and so allow us to ‘play (our) part’ at every stage in our lives.

REFERENCES


