INTRODUCTION

It is a great privilege to deliver the Tilak Venkoba Rao Oration during the ANCIPS 2002. It is an especial honour to have in the audience Professor A Venkoba Rao and Prof. Parvathi Devi, who have instituted this award in memory of their beloved son Tilak Venkoba Rao. They have always been a great inspiration to me, professionally and personally.

I would also like to acknowledge several of my teachers, especially Professors SM Channabasavanna, Rajat Ray and Nimesh Desai, who initially stimulated my interest in the area of alcoholism and Professors Mohan Isaac, Taranath Shetty and AB Taly for their constant support and encouragement. A lot of mutual learning has occurred through several post-graduates whom I have guided in dissertation, and I am indeed grateful to them all. I thank my family and close friends, especially J Sridhar, for their steadfast support in my professional pursuits.

Having been involved in clinical research in the area of alcoholism ever since my post-graduation, I have chosen to deliver this oration on certain biological and clinical correlates of alcoholism.

MAGNITUDE OF ALCOHOL CONSUMPTION

Alcohol ranks high as a cause for disease burden. The Global Burden of Disease project (Murray and Lopez 1996) estimated alcohol to be responsible for 1.5% of all deaths and 3.5% of total Disability Adjusted Life Years (DALYs). Despite the limitation in accurate and uniform data on the different aspects of alcohol use and related problems in India, two comprehensive reviews provide valuable insights into data available on various aspects of alcohol consumption, consequences and responses to the problem (Isaac 1998, World Health Organization 1999). A data bank maintained by the De-Addiction Centre (De-Addiction Quarterly 1996), NIMHANS, of treatment referrals to centres in Bangalore indicates that 95% of referrals are for alcohol related problems.

ALCOHOL RELATED PROBLEMS

Different alcohol consumption patterns are linked to a variety of health, occupational, psychological and social problems (Benegal et al 2001). Major neurological sequelae are discussed later. Tuberculosis continues to be an area of concern especially in chronic alcohol users from lower socio-economic strata (Harish et al 1999). A significant relationship has been established between high-risk sexual behaviour, HIV risk and alcohol use (Chandra et al 1999). Hepatitis B and C are underreported health problems in alcohol users (Saigal et al 2002). Even in the absence of manifest physical illness, quality of life can seriously be compromised (Chaturvedi et al 2000).

ALCOHOL AND SEIZURES

The etiology of seizures in alcoholism is diverse and includes central nervous system hyperactivity during alcohol withdrawal, aggravation of pre-existing epilepsy, associated central nervous system infections, systemic metabolic derangements and trauma (Johnson 1985). The overall prevalence of seizures in alcoholics has been calculated between 0.6-15% (Chan 1985). In India, prevalence of seizures among patients admitted primarily for alcohol dependence was 15% (Murthy et al 1999) and a study from Thailand reported a higher prevalence rate of 18.1% (Peng et al 1991). Patients with alcohol related seizures frequently have a family history of both alcohol dependence and epilepsy (Murthy et al 1999), suggesting that genetic factors may influence the susceptibility of certain alcoholics to neurological complications, including seizures (Kosobud and Crabbe 1986). The role of repeated abstinence in a kindling effect has also been suggested (Worner 1996). Imaging studies in alcohol related seizures reveal significant cortical atrophy, especially in the frontal (Meyer-Wahl and Brun 1982) and fronto-parietal areas (Murthy et al 1999).

ALCOHOL & NEUROLOGICAL DYSFUNCTION

Cerebellar signs, peripheral nerve involvement, and tremors have been commonly noted in asymptomatic alcohol dependents, even after withdrawal symptoms subside (Haridas et al 1997). Peripheral nerve disorders in alcoholics are predominantly polyneuropathies (Charness et al 1989) with symptoms and signs that reflect the involvement of sensory, motor and
autonomic nerves. Alcoholic neuropathy involves small as well as large diameter fibers, affects proximal as much as distal segments and is predominantly demyelinating in nature (Taly 2001). Alcoholic polyneuropathy is generally thought to result from inadequate nutrition (Victor et al. 1989), or from the direct neurotoxic effects of alcohol (Behse and Buchthal 1977).

**ALCOHOL AND NEUROPSYCHOLOGICAL IMPAIRMENT**

While cognitive impairments have clearly been associated with chronic alcohol use, there has been difficulty in establishing a distinct entity of alcoholic dementia (Lishman 1986). The information-processing deficits associated with alcoholic Korsakoff's syndrome have been extensively studied and are well established (Butters and Cermak 1980). More recently, evidence for a 'dysexecutive syndrome', characterized by impairment in visuospatial performance, mental set shifting, and the inhibition of habitual behaviour has been demonstrated in alcoholic patients with unimpaired memory and intelligence (Ihara et al. 2000). While psychomotor skills and short-term memory impairment improve significantly with prolonged abstinence, long-term memory remains impaired even after years of continuous sobriety (Brandt et al. 1983).

Social drinkers have also shown deficits in the area of immediate memory, psychomotor performance and abstract reasoning when compared to teetotalers (Andrade and Mukundan 1996). Alcohol dependence with no clinical evidence of malnutrition or neurological symptoms or signs of impairment also showed impaired visuospatial abilities (Shanmugiah 2001).

While mild to moderate cognitive impairment has been seen in 50-70% of chronic alcoholics across several studies (Molina et al. 1994), the etiology of alcohol cognitive deficits is uncertain, and nutritional deficiency has been postulated as a possible cause. There have been contradictory findings with respect to duration and quantity of drinking and the impact on neuropsychological functioning (Adams et al. 1984, Eckardt et al. 1995, Murthy et al. 2001).

**ALCOHOL AND NUTRITIONAL DEFICIENCIES**

Alcohol contains 'empty calories' and deficiencies of several vitamins and minerals have been associated with chronic alcohol use. The dietary intake of steady drinkers has been shown to be deficient in nutrients, especially thiamine (Victor et al. 1989). In India, despite the frequent co-occurrence of alcoholism and poor dietary intake, very few studies have examined this relationship. A dietary evaluation of alcohol dependent patients with no clinical evidence of malnutrition revealed that 60% of their calorie content came from alcohol. A 24-hour dietary intake revealed a diet deficient in protein, phosphorous, calcium, iron and thiamine. Biochemistry revealed raised serum pyruvate, indicative of a thiamine deficiency (Shanmugiah 2001). While this study found a negative correlation between pyruvate levels and specific test components of neuropsychological functioning, other results suggest that thiamine deficiency may not be the main pathogenic factor related to alcohol cognitive deficits (Molina et al. 1994).

**BIOCHEMICAL MARKERS IN ALCOHOLISM**

Many studies have examined the diagnostic role of gamma glutamyl transpeptidase, carbohydrate deficient transferrin and mean corpuscular volume as markers of state in alcohol dependent patients (Sillanaukee 1996). The aldehyde metabolizing enzymes, aldehyde dehydrogenases (mitochondrial and cytosolic), have also been evaluated as possible markers in alcoholism. Erythrocyte aldehyde dehydrogenase (EALDH) is a convenient peripheral marker of cytosolic aldehyde dehydrogenase. While the low EALDH demonstrated in chronic alcoholics during withdrawal normalized following abstinence (Jenkins 1982, Agarwal et al. 1985), Thomas et al. (1982) reported low EALDH levels even in abstinent alcoholics, suggesting its role as a possible trait marker. Murthy et al. (1996) demonstrated low EALDH levels in both alcohol dependent and their first-degree non-alcoholic relatives compared to controls. The EALDH values in alcohol dependent patients increased following abstinence, but tended to remain lower than in controls. In-vitro studies suggested the ability of benzodiazepines to activate EALDH, and overcome the inhibition of this enzyme by disulfiram (Murthy et al. 1992). This possibly explains the attenuated alcohol-disulfiram reaction in patients on benzodiazepines.

Genetic factors appear to play an important role in the risk for developing alcohol dependence. Genetics studies indicate that between 40 and 60 percent of alcoholism vulnerability has a genetic basis (Kendler et al. 1997). Allelic association of the polymorphism at the dopamine receptor 2 (DRD2) has been studied in alcohol dependent patients with conflicting results. Following the demonstration by Blum et al. (1991) of an association between alcoholism and the A1 allele, some studies showed a positive association between alcoholism and the Taq1 A allele at the DRD2 gene. A study in the Indian population did not show such a positive association (Shalik et al. 2001).

Several studies have hinted at protective alleles of alcohol dehydrogenase and aldehyde dehydrogenase isozymes, which act by precipitating an adverse response to alcohol intake (Chen et al. 1999). However, no difference in the allele frequencies at the ADH3 locus was found in a South Indian population with early onset alcohol dependence (Purushotham et al. 2001).

**WOMEN AND ALCOHOL USE**

In India, until recently, women were projected as victims of male alcoholism, or as powerful agents of community change, in movements against alcoholism. The problem of alcohol abuse among Indian women and its consequences is only gradually emerging. Evident features include a high family loading for alcohol dependence, frequent alcohol consumption in the spouse, different drinking expectations, a later onset of drinking with early health problems, frequent presentation with neuropsychiatric problems, frequent suicidal attempts (Murthy et al. 1995, Prasad et al. 1998, Murthy et al. 2009a) and distinct gender differences in initiating factors and effects of problem...
drinking (Selvaraj et al 1997).

TREATMENTS IN ALCOHOL DEPENDENCE

Since its serendipitous discovery as a deterrent for alcohol consumption in 1948, disulfiram, until recently, formed the mainstay of pharmacological treatment of alcoholism. It has now largely been overtaken by safer pharmacotherapies, primarily naltrexone and acamprosate (Spanagel and Ziegglansberger 1997, CNS Spectrums 2000).

With regard to non-pharmacological approaches, there is a strong argument for informed eclecticism in the treatment of alcohol problems (Miller and Hester 1989). Modalities such as individual therapy, group therapy, behaviour therapy and family therapy have all emerged as legitimate treatments and are often used in conjunction (Fehr and Douglas 1976). Project Match (1997) found similar patient treatment outcomes with Cognitive Behavioral Coping Skills Therapy, Motivational Enhancement Therapy and Twelve-Step Facilitation Therapy. Therapist moderated group therapy has been a poorly researched treatment modality for the treatment of alcohol dependence, but is perceived as being beneficial by a majority of patients (Kamath and Murthy 1998), and is a valuable adjunct to other treatment modalities.

FOLLOW-UP AND OUTCOME

Follow-up studies offer vital information regarding course and outcome of any illness. Follow-up in alcoholism is India is fraught with several practical difficulties. Novel tracing techniques are required for follow-up of patients with alcohol dependence lost to routine follow-up (Mahadevappa et al 1987). Robust long-term follow-up studies have been undertaken in the United States with very high percentages of follow-up (Schuckit 1994, Valliant 1996). In India, there have been mainly short-term outcome studies of clinical populations. Significant loss to routine follow-up has been a consistent finding, with major attrition in follow-up between 3 and 6 months (Prasad et al 2000). High abstinence rates (greater than 80%) were reported by Bagadia (1982) in patients available to follow-up, but Desai (1989) found more modest outcomes. Almost half the patients responding to follow-up 7.5 years after index treatment reported abstinence (John and Kuruvilla 1991). A four to five year follow-up of patients with alcohol dependence reported a mortality of 8.5 % (Sharma et al 1988). A much higher rate of mortality (40%) has been reported in a 10-12 year follow-up study of alcohol dependent with no serious systemic problem at baseline (Kena 2002).

There are few rating scales for comprehensive assessment in routine clinical follow-up of alcohol dependent. The Alcohol Severity Index (McLellan et al 1980) is a commonly used scale but is long and unwieldy for routine clinical use. A Brief Addiction Rating Scale (BARS), assessing functioning across 10 dimensions was evolved for routine clinical follow-up in the Indian population (Janakiramiah et al 1999).

Aftercare in alcohol dependence treatment is critical for better long-term outcome and several important issues related to aftercare need to be addressed (Murthy et al 2000b).

FUTURE DIRECTIONS FOR ALCOHOL RELATED RESEARCH IN INDIA

Davis and Sethi (1961) predicted, “in the march of industrialization and the change in social attitudes, concurrently there may arise a greater indulgence in alcoholic beverages”. There is indeed growing evidence worldwide from India of the increasing health, economic and social burden from alcohol. It is not enough for professionals working in the area to address issues of treatment and prevention. They have the additional responsibility of carrying out focused research that may guide in the prevention of this problem, facilitate early intervention and help in evolving cost-effective strategies for treatment and rehabilitation. Biological and psycho-social research need to be integrated to provide solutions to the myriad problems associated with alcohol. There is a need for focused research in the area, which can be translated into prevention and clinical practice.

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