DISCUSSION

This prospective case control study was conducted at Bir hospital, Kathmandu, between August 1998 to July 1999. Situated in the heart of the Kathmandu city the hospital mainly serves as a tertiary care centre for patients from all parts of Nepal. Nephrology Department of the hospital has been providing renal biopsy services, intermittent peritoneal dialysis, emergency and maintenance hemodialysis services to the Nepali population.

A total of thirty nondiabetic chronic uraemics on maintenance hemodialysis were studied for autonomic dysfunction along with age matched nineteen healthy controls. The charts of uraemics were reviewed to find out the cause of CRF. Since many patients presented very late in their illness with small, shrunken kidneys from which no informative renal tissue could be obtained, the cause of CRF could not be established in six uraemics from the charts.

A resting tachycardia and a fixed heart rate have often been regarded as characteristic of cardiovascular denervation in the diabetic population. Ewing et al\textsuperscript{7} also stated that absence of sinus arrhythmia could be used as a screening test for the presence of autonomic neuropathy even in uraemics. In accordance Chopra et al\textsuperscript{80} and Agarwal et al\textsuperscript{100} also showed a significant rise in basal heart rate of nondialysed uraemics in comparison with the controls. But Heidbreder et al\textsuperscript{82} in their study could not demonstrate any significant rise in basal heart rate in both nondialysed and dialysed uraemics. This study also failed to show any significant rise in basal heart rate in dialysed uraemics when compared to the controls.

This study revealed a significantly increased resting systolic and diastolic BP in uraemics than the controls supporting the results of Chopra et al.\textsuperscript{80}

Clinical Symptomatology
Ewing & Winney,7 Malik et al,4 and Heidbreder et al,82 in their studies documented the presence of abnormal cardiovascular reflex tests in uraemics but failed to show significant symptoms of AN in them. However, Vita et al,83 found several symptoms suggestive of AN in uraemics they studied though such symptoms were not present in all patients with test proved autonomic derangement, and in addition some uraemics had positive symptoms but normal tests. The present study also showed presence of one or the other symptoms of AN in all the chronic uraemics though all of them did not have abnormal tests. In this study, no assessment was made of impotency. These findings show how inaccurate it is to rely on subjective symptoms. The clinical symptomatology is often nonspecific and most of them do not concern the cardiovascular reflexes.

**Cardiovascular reflex test abnormalities**

Several studies indicate the occurrence of autonomic dysfunction in uraemics on hemodialysis which varies between 50% - 92%.7,14,80 Vita et al,83 however, in their study demonstrated only a 40% incidence of autonomic dysfunction in chronic uraemics on MHD and explained that the relatively low value could be due to their use of age-adjusted normal ranges. This study showed involvement of ANS in 80% of the uraemics. Valsalva ratio, heart rate response to deep breathing and standing were abnormal in 53.33%, 56.67% and 56.67% of uraemic patients respectively in this study whereas systolic BP fall to standing occurred only in 30% of the patients. The results in this study indicate that damage to cardiovascular autonomic reflexes is widespread in patients with CRF with cardiac vagal abnormalities being more striking than peripheral sympathetic involvement. The tests used measure overall cardiovascular reflex function and do not localise lesions to afferent, efferent or central parts or the reflex arc. Studies till date7,14,80,82,83,102 have confirmed that parasympathetic involvement is more common than sympathetic involvement in uraemics.

Diastolic BP response to sustained handgrip was found to be abnormal in 50% cases, an incidence slightly higher than the reported ones. Since many of the chronic uraemics in this study could not maintain the handgrip at 30% of their maximum voluntary contraction for more than 2 minutes, the rise in their diastolic BP would not have been up to the expected level giving rise to the abnormal results. In all uraemics for sustained handgrip test the difference between the blood
pressure just before release of handgrip and before starting was taken as the measure of the response irrespective of the time they maintained the handgrip.

Out of the 19 healthy controls, one 53-year-old female and the other 66 year old male showed borderline results of Valsalva ratio and heart rate response to deep breathing respectively. The test results in these elderly patients support the statement that tests of vagal function e.g.; Valsalva ratio, the heart rate responses to deep breathing, standing, and baroreceptor sensitivity have a negative linear relationship to age. Since the age-adjusted normal ranges of these tests were not taken into account in this study, it could have been that the borderline results were normal for their ages. None of the controls demonstrated any evidence of autonomic dysfunction when the test results were grouped to grade the severity.

**Comparison between cases & controls**

When the autonomic function tests were compared between controls and chronic uraemics, the results of Valsalva ratio and heart rate response to deep breathing were significantly low in uraemics supporting the view that uraemia itself is responsible for AN. However, the normal range for heart rate response to standing i.e. 30:15 ratio, had a lower limit which made it impossible to separate any patients with abnormal responses. Therefore, the difference in 30:15 ratio between the control and chronic uraemics was not significant.

O' Brien et al in their study found that out of 294 normal subjects, 43% had a 30:15 ratio less than 1. Strictly, the 30:15 ratio takes the shortest R-R at or around the 15th beat and the longest at or around the 30th beat. The results will obviously depend on how forward the 15th beat and the 30th beat the net is cast.

**Influence of age**

When the control population was divided into two groups aged 16-35 years and >35 years group, it was seen that all the heart rate tests were significantly low in the >35 year age group while
chronic uraemics aged >35 year had significantly decreased Valsalva ratio compared to 16-35 year age group showing that parasympathetic responses deteriorate with age. When both controls and chronic uraemics of 16-35 year and >35 year age group were compared, the parasympathetic tests were still significantly lower in uraemics showing that there is residual effect of uraemia on parasympathetic nervous system.

Contrary to the results of a study done by Vita et al in 1987, this study could not demonstrate significantly decreased rise in DBP to sustained hand grip in elderly uraemics. Such data could have been the result of not using age-adjusted confidence limits due to feasibility reason and low sample size. However, results can be explained on the basis that sympathetic tests do not have any relation with age.

**Influence of duration of dialysis**

Duration of dialysis did not have significant relation with abnormal autonomic testing in this study as demonstrated by Agarwal et al. In this respect hemodialysis treatment did not appear able to stop the progression of the disease. However, influence of the duration of underlying nephropathy before starting hemodialysis cannot be excluded.

**Association with peripheral neuropathy**

In this study 30% of the chronic uraemics showed definite peripheral neuropathy when positive sensory symptoms, positive sensory signs and absent ankle jerk were taken into account but objective testing (nerve conduction studies) was not done in the present study.