Discussion
DISCUSSION

With the remembrance of anaesthesia, during 1930s, and 40s, the statement, that modern anaesthesia owes its existence to the introduction of muscle relaxants in clinical practice, can not be disagreed upon. Hence it would not be out of order, if one can say that the use of curare in 1942, by Griffith and Johnson at Montreal, marked the dawn of modern anaesthesia.

The initial success of curare led, in the subsequent years, to the introduction of many synthetic and semisynthetic neuromuscular blocking agents which were soon dropped like hot potatoes, blaming them not to be as safe as were previously thought. This was due to the fact, that there was a significantly higher mortality rate in patients receiving these drugs, a finding which was startling to the world and led to a lot of controversy.

An inherent drug toxicity was thought to be the cause as ascribed by Beecher. However, with the present understanding of neuromuscular blocking mechanism, a possible explanation to this high mortality rate, could be the then unrecognized residual paralysis, leading thereby to post-operative respiratory insufficiency, coupled with non-realization of the importance of antagonism of these drugs.

The above explanation gains its support from the fact that subsequent understanding of the importance of maintenance of adequate pulmonary ventilation during neuro-muscular blockade and its antagonism by neostigmine led to a
tremendous fall in the mortality rate following these drugs and thus the concept of "balanced anaesthesia" came into being. But with the use of neuro-muscular blockers, surgeons also complained of unsteady muscular relaxation during the surgical period, leading to frequent repetition of maintenance doses. Simultaneously, as the scope for anaesthesiologists was increasing in the intensive care units, this also demanded requirement of these drugs for prolonged periods, in patients who were kept on ventilators. Once again a hunt was on to synthesize more safe drugs, in terms of shorter duration of action, no organ specific adverse effect and no organ-dependent elimination from the body, so that they could be given by continuous infusion method, to achieve a constant plasma level throughout the surgery, with no residual paralysis after the cessation of their use and rapid recovery.

Many pharmacodynamic models were developed to evaluate safety and efficacy but only Atracurium and Vecuronium could prove their merits, considering their shorter duration of action, no systemic side effects and no residual action after being used by continuous infusion. (Marguer A, Gangarini, Salvatore J. Basta, Severese J. John, 1994, Mirakhar RK, Ferres C, J. Pandit SK, 1982)

During the present study, Atracurium and Vecuronium were chosen to provide muscle relaxation, because they have been shown to possess most of the properties of an ideal neuro muscular blocking agent.

The study was designed to minimize interacting influences such as medical status, premedication, anaesthetic drugs, surgical manipulations and duration of surgery (Table III & IV).

The mean age and weight of the patients were similar in all the groups. (Table I & II)
On set of action (Table V)

The onset of action in Atracurium intermittent bolus and continuous infusion groups (i.e. I A and II A) was 6.04 and 6.12 min respectively, while in vecuronium II A and II B groups, this was significantly shorter (3.93 and 3.81 min respectively).

It is worthwhile to mention here that this onset time (i.e. from injection to the peak effect) was noted, after a loading dose of 2xED95 and peak effect was judged by suppression of all four twitches in response to TOF stimuli, which was measured by ulnar nerve stimulation at the wrist.

E N Robertson, L H D J Baar, R J Hagen and J F Wood (1983) reported onset time for vecuronium and atracurium 1.7 min and 1.67 min respectively when the drugs were used in the doses of 1xED94 where as it was 2.8 to 3.5 min in a dose of 3xED90. A possible explanation to this discrepancy can be that the time to develop maximum blockade at peripheral sites is more than that provided by these agents to facilitate intubation, as vocal cord relaxation is seen much earlier than the peripheral suppression of all four TOF stimuli, more over these workers had used 3xED90 doses to evaluate the intubating condition, as against 2xED95 during the present study.

G Noelde, H Hinsken and W Buzello (1984) have reported onset time of vecuronium 3.4 ± 2.4 min after a loading dose of 0.075 mg/kg.

SURGICAL CONDITIONS

These were assessed both clinically and by visualizing suppression of twitches in response to TOF stimuli. Muscular relaxation was excellent in more than 80% of cases in all the groups (Table VI).
During the present study, it was noted that although, the time interval between any two maintenance doses in all the cases, was almost constant (10.68 min in IA and 10.33 min in II A), thereby showing no cumulative property of these agents, (Table VII), but condition provided by intermittent bolus groups were not constant. There was waxing and waning of muscular relaxation with the recovery of blockade, as was also shown by return of response to TOF stimuli, thus demanding for frequent repetition of maintenance doses of non-depolarizing agents in their respective groups, where as in group IB and II B, there was constant suppression of twitches in response to TOF and a steady state of muscular relaxation was achieved. Thus as the continuous infusion was started 10 to 15 min after the loading dose, this probably provided constant plasma levels and better surgical conditions as compared to intermittent bolus groups, where plasma concentration was fluctuating and surgical conditions were not stable.

F N Robertson and R J Fragnes (1984) compared atracurium and vecuronium given in the doses of 3XLD90 and concluded that blocks produced by these were 85.3 ± 4.0 and 90.9 ± 2.5 %.

The present study also confirms the suggestions of previous studies that time required to stabilize neuro-muscular blockade depends on the loading dose, on the time interval between loading dose and commencement of infusion and on the rate of infusion. It has been suggested by previous workers that as a basic approach, for stable 90% block the loading dose should be in the order of 1.5-2X ED 90, the same dose should be infused per hour and infusion should be started within first 10-15 min after injecting the loading dose. (G Noeldeke, H Hunsken and W Buzello 1984)

**CARDIOVASCULAR PARAMETERS:**

Pulse rate, systolic and diastolic blood pressures and mean arterial pressure (i.e. Diastolic + 1/3 of pulse pressure) were compared at different intervals after the administration of atracurium and vecuronium intermittently or during infusion.
Changes in Pulse rate (Table VIII)

A marked rise in the pulse rate, by a margin of 14%, was observed in all the cases following intubation, during the present study. This beyond doubt, was a normal response to laryngoscopy and intubation and 10 min after which a fall was recorded, till it came down to its basal value at the 30th minute. However after 1 hr, a decrease by 2-3% was observed in groups IA and IIA & IIB. Surprisingly, this decrease was not seen in group IB, where it remained elevated by the same margin.

An interesting finding noted during the study was that there was again a rise in pulse rate at 1 1/2 hrs, and before reversal in both the infusion groups. This rise was not seen in intermittent bolus groups.

Atracurium and vecuronium have been found to be free from direct cardiovascular responses. The lack of any chromotropic effect with these drugs may allow the heart rate to decrease. However intra-operative bradycardia after vecuronium has been described by Salmenpera et al. (1983) and it was thought to result from lack of antagonism of vagotonic influences such as anaesthetic drugs or surgical maneuvers. Similar findings have also been reported by Barnes et al. 1982, E.N Robertson, I.H.D.J Boony and R.J Fragen in 1983. But these workers did not find any increase in pulse rate after atracurium.

Although there can be many causes of increased heart rate intra-operatively, the possible explanation to this finding during the present study, could be, that although there were no conclusive evidences, but possibly slight histamine release was there, which was sufficient to increase the pulse rate but was not enough to cause clinically evident syndrome of histamine release. Various workers have reported that this syndrome might become evident clinically when histamine levels increase to over 1000 pg/ml (details under the sub-title histamine release). Probably these high levels were not achieved during the present study and therefore all other
signs and symptoms of histamine release were not seen. But as it is a possibility with the use of atracurium, the subject needs further studies and evaluation.

Increase in pulse rate at 1½ hrs and just before reversal in infusion groups could be explained by the fact that in most of the cases as the surgery was near its completion and infusion pump was stopped 10 mins before anticipated time of completion, a gradual recovery from the blockade resulted in an increase in heart rate.

**CHANGES IN BLOOD PRESSURE AND MEAN ARTERIAL PRESSURE:**
*(Table IX, X & XI)*

As with the pulse rate, a 10 - 15% increase in systolic blood pressure and 6-10% increase in mean arterial pressure was observed in all the groups after intubation which may be regarded as a normal response to laryngoscopy and endotracheal intubation. Pressures remained elevated till 5 mins after the loading doses of relaxants in their respective groups. After incremental doses and starting infusion i.e. after 10 to 30 mins, systolic blood pressure returned to its basal value or there was 1-2% decrease as compared to preoperative recordings and then it remained almost constant throughout surgery. Similar values were obtained for mean arterial pressure. In both the infusion groups a slight increase in systolic blood pressure was recorded at 1½ hr and before reversal. These findings were parallel to changes in pulse rate and thus confirmed that it was due to gradual recovery of blockade as the infusion was stopped by this time.

These findings coincide to Lavery et al (1987) who concluded that vecuronium caused no significant changes in systolic blood pressure & mean arterial pressure.

Boon, Fragen and Crul (1987) have also reported no significant changes in heart rate and arterial pressures with atracurium and vecuronium. In their study,
there was statistically significant decrease in mean arterial pressure but this was small (4-5%) and was not considered clinically significant. Similar alterations have also been noted by Barnes et al in 1982.

E.K.G. CHANGES: -

E.K.G changes in lead II were compared in Atracurium & Vecuronium intermittent bolus groups and infusion groups and it was found that both the drugs caused no abnormality in cardiac rate or rhythm. As these agents have been found to be relatively free from direct cardiovascular action, these agents can be considered safe in relation to any cardiac adverse effects. These conclusions are coincidental with those of Boon F H D J, Edwards R C, Smith S and Miller R D 1981 and Bowman W C 1982.

HISTAMINE RELEASE:

Conclusive signs of histamine release, for example, unexplained slight to moderate rise in heart rate with erythema of the face, neck and upper torso, rashes, and fall in arterial pressure and bronchospasm were not found in any case during the study. In Atracurium infusion group slight rise in pulse rate was noted in the absence of any other obvious cause, which may be because of slight release of histamine but no other signs were noted. Vecuronium is virtually free from histamine releasing property. It has been shown that it does not release histamine throughout a wide clinical dose range from one to eight times the ED95 (i.e. 0.05 to 0.40 mg/kg). Morris R B, Cahalan M K, Miller R D et al, 1983, Tulloch W C, Diana P, Cook D R et al, 1990.

Although Atracurium as a benzylisoquinolinium compound may cause histamine release, Hughes and Chapple (1981) reported that Atracurium caused clinically evident histamine release only when 8-16 times the neuro-muscular blocking dose was used intravenously. During the present study, there was no clinical evidence of histamine release after the injection of drug.
According to Basta S.J (1990), Severence M. and Ali H.H et al (1983), the syndrome of histamine release may become clinically evident when doses of two times ED95 or more are injected rapidly. When plasma histamine levels increase to over 1000 pg/ml, a transient decrease in blood pressure, together with facial erythema may be noted. This can be prevented by slower injection of atracurium over 30-60 sec and by the use of combined H₁ and H₂ receptor blockade (Hoskin et al. 1988). Scott et al (1985) have also suggested similar findings.

RECOVERY OF BLOCKADE (Table XII & XIII): -

The time taken from last intermittent bolus dose or from stopping the infusion to 25% recovery of the blockade was 10.44 ± 1.65 sec and 8.96 ± 2.12 sec respectively in Atracurium (IA & IB) groups and 11.02 ± 2.38 & 11.12 ± 2.25 sec respectively in groups IA & IB while that taken for full recovery from reversal in its usual dosage was 8.18 sec and 10.8 sec in groups IA and IB respectively and 9.04 and 14.2 sec in corresponding vecuronium groups. Thus the time for full recovery was significantly more in vecuronium infusion group. There were no signs of residual blockade or recurarization in any case.

The pharmacodynamics of Atracurium and Vecuronium correspond to previously reported studies by Payne & Hughes (1981) and Cruij & Bootj (1980). The reproducible recovery rate of Atracurium, found in the present study, has been commented on before (Payne & Hughes 1981, Hughes & Chapple 1981). The prolongation of the recovery rate of Vecuronium has also been noted in other studies (Agoston et al., 1980) but has been considered to be insignificant. If Vecuronium terminates its effects by redistribution as suggested by several pharmacokinetic studies (Agoston et al., 1977, Bootj et al 1981), the prolonged recovery rate might suggest that the distribution volume is becoming saturated at these doses. If even greater doses of vecuronium were used, the increase in the duration of recovery may
lead, possibly to prolongation of the total duration of action. In contrast the steady recovery rate of Atracurium might suggest that the metabolic pathways thought to terminate its effects (Hofmann elimination and ester hydrolysis) are not saturated at the doses used.

Sohn and colleagues (1982) proposed a three compartment pharmacokinetic model where the uptake of the unchanged vecuronium was the main principle controlling the recovery of neuromuscular transmission, and it may be assumed that the infusion provides a more effective saturation of the third compartment than do intermittent injections. d'Hollander and colleagues (1982) observed stable neuromuscular blockade 40 mm after the injection of the loading dose and only 9 ± 4 mm elapsed from the end of infusion until recovery of 25% of control twitch tension. The results with the infusion of atracurium were similar to the findings with the continuous administration of Vecuronium in study carried out by d'Hollander in 1983, except for the recovery time which was 7 mm shorter with atracurium than with vecuronium. This difference may be a result of their different metabolic disposition. Hofmann elimination is the major metabolic pathway controlling the duration of action of Atracurium (Hughes & Chapple 1981). In contrast, Vecuronium undergoes redistribution and excretion with very little metabolic degradation (Sohn et al 1982). Apparently, under the conditions of continuous infusion, the metabolic pathways of Atracurium are more effective in rapidly restoring neuro-muscular transmission than with Vecuronium.

It can therefore be said that both atracurium and vecuronium have provided the modern anaesthetists with the very precious tool to their already vast armamentarium, as is evident by their safe pharmacodynamics over wide ranges of dosage. These drugs no doubt have a promising horizon particularly with their use as continuous infusion.