DISCUSSION
The introduction of neuroleptics into clinical anaesthesia has put one of the largest feathers in the cap of anaesthesiology. It was a remarkable success achieved by the anaesthesiologist so far. It has much to boast about, as regards its utility in clinical practice. Leave aside the neurovegetative block and analgesia it produces, its popularity lies in the fact that it provides a very wide coverage of all types of patients and operations in almost all age groups, coupled with the outstanding stability of vital functions and maintenance of physiology to near normal, while nothing to say about the scope of an easy control over the level of anaesthesia.

The analysis of observations made during and after the administration of neuroleptanaesthesia to 116 patients, belonging to age group of 12–65 years, of both sexes (61.2% male and 38.8% female) undergoing major operations (Table II), induced with single dose of Droperidol and fractional doses of Fentanyl and or Pentazocine, nitrous oxide-oxygen and muscle relaxants revealed the following facts.

Induction of anaesthesia with neuroleptics was slower than the other conventional intravenous anaesthetic techniques. Mean induction time was maximum (15.2 minutes) when Droperidol and Pentazocine (Group B)
were used together with nitrous oxide - oxygen as a modified method of neuroleptanaesthesia while it was 13.25 and 13.9 minutes when Droperidol and Fentanyl were used together with nitrous oxide and oxygen in group A and C respectively. Our findings of slow induction with neuroleptanaesthesia is in conformity with Corssen and coworkers (1964), Foldes et al (1966) who observed that when 3 litres minute⁻¹ nitrous oxide and 1 litre minute⁻¹ oxygen mixture was administered for 6-10 minutes, after Fentanyl and Droperidol, skin incision was well tolerated.

Prolong induction time with Pentazocine could be attributed to lesser potency of Pentazocine as compared to Fentanyl. The course of induction was smooth in majority of the patients (97.5% in Group A, 86.0% in Group B and 92.5% in Group C). 13.9% incidence of prolong and stormy induction was maximum with Pentazocine (Group B), 7.5% with Fentanyl and Pentazocine (Group C) and 2.5% with Fentanyl (Group A). This observation is in accordance with the views of Holderness et al (1963), Corssen et al (1964) and Foldes et al (1970). Holderness et al (1963) were of the view that mild to moderate excitement during induction was partially related to the time of starting nitrous oxide. If inhalation was begun too early before sedation had developed, there was a greater likelihood of excitement.
Stormy induction was chiefly found in patients in the age group of 25-34 years, particularly persons indulged in alcohol and other intoxicants. Foldes et al (1970) found that these patients required increased doses of the anaesthetics and has reasoned it to be because of two factors:

1. Habituation to those drugs decreases the sensitivity of brain to all CNS depressants.
2. Both narcotics and barbiturates cause enzyme induction which results in rapid biotransformation of these agents.

To hasten the induction in these cases thiopentone sodium 100-150 mg was given intravenously. To make the patient unconscious Iwatsuki et al (1971) had suggested the use of minimal dose of thiopentone sodium or minimal concentration of halothane in this modified technique of neuroleptanaesthesia with Droperidol and Pentazocine.

Frequency of doses of analgesic drugs required was maximum (95%) in group A, out of which 72.5% of patients required 2-3 doses of Fentanyl and few of them needed upto 5 doses (Table III A). In group B 63.9% cases required single dose only, given at the time of induction of one dose only (Table III B). In group C, 55.7% patients required a single dose of both the drugs, 37.5% of patients needed repetition of Fentanyl once
only (Table III C). This frequency of doses was dependant on duration of surgery. Holderness et al (1963) have made similar observations and stated that some patients required additional doses at every 15 minutes interval, while in others, dose interval exceeded 60-75 minutes. More frequent administration of Fentanyl than Pentazocine in similar duration of surgery indicates shorter duration of action of Fentanyl than Pentazocine, similar views were also expressed by Iwatsuki et al (1971).

Cardiovascular effects:

In our study administration of Droperidol in all the three groups of cases has caused an insignificant rise in mean pulse rate (p > 0.05) over control values obtained before induction of anaesthesia. This confirms the views of Foldes et al (1970) and Sonntag (1973). All patients had normal sinus rhythm on electrocardiography.

Subsequent injection of Fentanyl caused insignificant change in mean pulse rate (Group A + C) and at the end of anaesthesia also it was similar to control value, the difference between the two being statistically insignificant. Similar observations were also reported by Holderness and chase (1963) and Foldes et al (1970). The rhythm remained regular throughout the course of anaesthesia in all the patients of group A and C.

Two patients in group A and one in group C developed sinus tachycardia, which started at the time of intubation
and persisted throughout the course of anaesthesia. In these cases induction was prolonged and stormy. This change in pulse rate persisted even after deepening the level of anaesthesia by further administration of Droperidol and Fentanyl. This may be probably due to stimulation of sympathetic reflexes at the time of intubation. Foldes et al (1970) encountered hypertension in some cases which was accompanied by rise in pulse rate and respiratory frequency indicating inadequate analgesia, which could well be corrected by administration of analgesics. They however maintain that this could persist without any sign of inadequate analgesia which could be corrected by hypotensive drugs.

Electrocardiographic changes were insignificant even in patients who were given local adrenaline infiltration for hemostasis. This is explained on the basis of classical alpha-adrenergic blocking action of Droperidol (Janssen et al, 1963, Schaper et al, 1963, Yelnosky et al, 1963 and Whitwam and Russell, 1971).

Subsequent injection of Pentazocine after Droperidol (group B) caused a fall, though insignificant in mean pulse rate (p > 0.05). At the end of anaesthesia, there was further slowing of mean pulse rate (p < 0.01) which was significant statistically. Slight bradycardia with the use of Pentazocine has also been reported by Potter and Payne (1970) during nitrous oxide and
halothane anaesthesia. Contrary to this Sadove et al (1964), Ahlgren and Stephen (1966) and Norris and Telfer (1968) observed rise in blood pressure accompanied by slight tachycardia in conscious patients after Pentazocine.

Droperidol caused an insignificant decrease of systolic and diastolic blood pressures (p > 0.05). A slight fall in blood pressure was also reported by Corssen (1964), Haase and Janssen (1965) and Foldes et al (1970), and is said to be due to fall in peripheral vascular resistance, secondary to alpha-adrenergic blockade and also to direct peripheral vaso-dilatation. There is no direct myocardial depression (Corssen, 1964).

Subsequent administration of Fentanyl in group A and C did not significantly alter the mean systolic and diastolic blood pressure (p > 0.05). This is in accordance with the reports of Holderness et al (1963), Dobkin et al, (1964) and Foldes et al (1970). However Fentanyl had been blamed to cause hypotension as reported by Larson (1963), Gordocki and Yelnosky (1964) and Gordotzky and Martin (1965) which last for few minutes (Brown 1965). Contradictory to this Macdonald et al (1966) and Pryse-Roberts and Kelman (1967) reported insignificant rise in mean arterial pressure.

Two patients in group A and one in group C developed sustained rise in systolic blood pressure,
associated with increase in pulse rate indicating insufficient analgesia or anaesthesia, an indication for the administration of additional doses of Fentanyl. But this systolic hypertension persisted even on deepening the level of analgesia with Fentanyl or making the patient more tranquil with Droperidol. Rise in mean arterial pressure was also observed by Macdonald et al (1966) and Prys-Roberts and Kelman (1967) which they attributed to the concurrent hypercapnoea during spontaneous ventilation, rather than a direct effect of analgesic drug. In our study blood pressure and pulse rate did not come to normal values even on hyperventilating the patients, thereby ruling out the possibility of hypercarbia and/or hypoxia. The precise cause of this hyperdynamic response to neuroleptanalgesic is not fully understood. The evidences available so far are quite debatable as Giesecke et al (1967) believes that Fentanyl stimulates the release of epinephrine, as shown by increased urinary output of epinephrine in man, while Iverson (1965) has blamed Droperidol, stating that it like other alpha-adrenergic blocking drugs decreases the tissue uptake of epinephrine and non-epinephrine.

Marked hypotension was seen only in one patient undergoing splenectomy under classical method of neuroleptanaesthesia (Group A) who had severe blood
loss, but the peripheries remained well perfused and warm probably due to alpha-adrenergic blocking action of Droperidol. It confirms the view of Schaper et al (1963) who also reported selective blockade of alpha-receptor of the sympathetic nervous system and therefore suppressing the vasoconstrictive action of catecholamines with the use of Droperidol.

Subsequent injection of Pentazocine after Droperidol (Group B) and after Pentanyl (Group C) caused insignificant increase in systolic and diastolic blood pressure ($p > 0.05$) which persisted till the end of anaesthesia, confirming the views of Kay and coworkers (1970) and Iwatsuki et al (1971). However, Keats and Telford (1964) and Brown (1969) reported rise in blood pressure with the use of Pentazocine in doses of 2 mg/kg in conscious patient. Potter and Payne (1970) observed a significant rise in mean arterial pressure of 9.5±4.9 with a dose level of 30 mg intravenously in conscious adults. Similar observations were made where Pentazocine was given during anaesthesia with nitrous oxide and halothane. The cause of this hypertensive effect, whether increased peripheral resistance or increased cardiac out put is not well established (Tammisto and colleagues, 1970) but the pallor observed after higher doses argues in favour of the former mechanism. However, Kay and coworkers (1970)
did not observed any systemic hypertensive response when
they used Pentazocine in conjunction with Droperidol,
which they say might be due to alpha-receptor blockade
produced by Droperidol.

Respiratory changes:

Droperidol caused an insignificant fall in mean
respiratory frequency (p > 0.05) in all the three
groups (Table VIII A, B and C). This is in accordance
with the observation of Corssen et al (1966) and
Foldes et al (1970). Although there was no significant
change in mean tidal volume (p > 0.05), a significant
fall in mean minute volume (p < 0.05) was registered
after administration of Droperidol in all the three
groups (Table IX, A, B and C). Foldes et al (1966) have
also reported minimal respiratory depressant effect of
Droperidol in doses of 0.10-0.15 mg kg⁻¹. This minimal
fall in ventilatory efficiency due to Droperidol may be
attributed to the psychomotor sedative action of the
drug as has been suggested by Prys-Roberts et al (1967).
However, Schaper et al (1963) and Yelnosky et al (1963)
have stated "the effect of Droperidol on respiration is
slight, by increasing respiratory volume relatively high
doses of Droperidol, improve effective ventilation and
oxygen saturation".

Subsequent administration of Fentanyl caused
marked respiratory depression as evident by highly
significant fall in mean respiratory frequency, tidal volume and minute volume (p ≤ 0.001 in all cases). This confirms the observations of Holderness et al (1963), Foldes et al (1966) and Corssen and coworkers (1966). In contradiction to our findings, Prys-Roberts and Kelman (1967) observed fall in respiratory frequency, minute volume and alveolar ventilation despite a compensatory increase in tidal volume. The lack of compensatory increase in tidal volume, in our study could be explained by the fact that the respiratory centres, under the effect of Fentanyl become insensitive to the PCO₂ levels as also suggested by Magoun (1963).

However, Jennett et al (1968) are of the opinion that there is a decrease in expiratory minute volume rather than in the frequency following administration of Fentanyl in conscious patients.

Apnoea was noted in 22.5% of cases in group A and 10% cases in group C (Table XII), 2-3 minutes after intravenous injection of Fentanyl prior to intubation. During this period patients remained conscious and responded adequately to verbal commands to breathe. Controlled respiration for a short period provided effective ventilation without loss of analgesia as also shown by Corssen et al (1966) and Prys-Roberts and Kelman (1967).
42.5% of cases in group A and 35% in group C developed ventilatory difficulty (Table XII) due to chest wall rigidity after Fentanyl administration. Holderness and coworkers (1963) also reported similar findings after rapid intravenous injection of Fentanyl. This ventilatory difficulty was readily counteracted by intravenous administration of succinylcholine thereby agreeing to the findings of Holderness et al (1963). Corssen (1966) says that "although this period does not last for more than 3-5 minutes and subsides spontaneously, it can be rapidly overcome by intravenous administration of succinylcholine".

Administration of Pentazocine following Droperidol (Group B) also caused highly significant fall in mean respiratory frequency, tidal volume and minute volume (p < 0.001 in all cases).

A small dose of Pentazocine subsequent to Droperidol and Fentanyl (Group C) caused just significant fall (p < 0.05) in respiratory frequency and highly significant fall (p < 0.001) in mean tidal and minute volume.

Similar observations were made by Kay and coworkers (1970) and Iwatsuki et al (1971).

The degree of ventilatory depression was more marked with Fentanyl as compared to Pentazocine. Apnoea or ventilatory rigidity was also not seen with Pentazocine which also confirms the observation made by Kay and coworkers (1970) and Iwatsuki et al (1971).
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This ventilatory depressive action of Fentanyl and Pentazocine persisted till the end of anaesthesia. But the fall in mean minute volume at the end of anaesthesia from that of control level was significant in group A (p ≤ 0.01) highly significant in group B (p ≤ 0.001) and insignificant in group C (p ≥ 0.05).

That the significant fall in mean minute volume at the end of anaesthesia with Droperidol and Fentanyl (Group A) was also observed by Prys-Roberts and Kelman (1967) who have stated "although the ventilatory depression occurring during neuroleptanaesthesia may be prolonged into the postanaesthetic period, the blood gas tension, acid base state after neuroleptanaesthesia do not differ significantly from those found after other anaesthetic techniques".

A highly significant fall in mean minute volume persisting at the end of anaesthesia with Droperidol and Pentazocine (Group B) could be attributed to the longer duration of respiratory depressive action of Pentazocine, thereby making controllability of anaesthesia difficult, as also reported by Iwatsuki et al (1971).
An insignificant fall in mean minute volume at the termination of anaesthesia with Droperidol and Fentanyl followed by a small dose of Pentazocine could be attributed to weak narcotic antagonistic action of Pentazocine as suggested by Harris et al (1964).

Administration of Nalorphine in 17.5% cases in group A showed effective reversal of postanaesthetic respiratory depression (Table X and XI). Foldes et al (1965) Prys-Roberts and Kelman (1967) and Foldes et al (1970) have also used Nalorphine with marked success in counteracting the respiratory depression after Fentanyl.

Doxapram was tried in 11.1% of cases in group B and 17.5% in group C who were having respiratory insufficiency. The end results were found to be quite gratifying as assessed by an increase in respiratory rate and minute volume compared to the end anaesthetic values.

Yamato (1973) while studying the effect of Doxapram on ventilation after neuroleptanaesthesia observed that tidal volume and respiratory resistance increased twice as high as the level before administration by rapid single shot of 1 mg/kg of Doxapram but after 5 minutes it returned to control levels. When Doxapram 6 mg/kg was infused for 30 minutes, the minute volume stayed higher and Pa CO₂ stayed lower.
than the control levels even after 60 minutes. Wakushima et al (1974) found significant increase in tidal volume after injection of Doxapram, though respiratory rate remained unchanged. The onset of effect of Doxapram was seen within 1 minute of intravenous injection and the effect lasted for about 15 minutes.

Mean recovery time (Table XII) after discontinuation of nitrous oxide administration was approximately the same being 5.12, 5.14 and 5.47 minutes in group A, B and C respectively. This compares favourably with the observations made by Iwatsuki et al (1971). In his study recovery from anaesthesia was also rapid. At the termination of operation, patients were able to respond to simple questions and were painfree, this analgesic effect lasted for a considerably longer duration, in post operative period. Patients were tranquil and co-operative in recovery room. Holderness et al (1963) also reported similar results in their study where most of the patients recovered within 15 minutes. Emergence from anaesthesia was smooth, patient awakened peaceful, free of pain and able to converse rationally. Although consciousness and orientation returned soon after discontinuance of nitrous oxide, many patients were drowsy for a number of hours thereafter, sleeping lightly, unless aroused, at which time they could converse intelligently. Holderness et al (1963),
Foldes et al (1966) and Pryse-Roberts (1967) noted few patients complaining of mental depression and inability to concentrate during the remainder of the day of operation, as occurred in 11.1% of cases in the present study (Table XV).

Incidence of extrapyramidal muscular twitchings and motor excitement was infrequent (Table XII) occurring at the time of induction in one patient of group A and three in group B. Corssen et al (1966) also observed extrapyramidal muscular twitchings in 5 cases in a series of 510 cases. Dobkin (1964) observed severe extrapyramidal excitation though occasional, developing in post operative period. Holderness et al (1963) reported that the transient undesirable neuromuscular reactions were common in younger age group. Patton (1975) observed that most extrapyramidal reactions caused by Droperidol are of dyskinetic type usually occurring in recovery period. He concluded that these extrapyramidal reactions tend to disappear following administration of benztropine or atropine. None of the patient in our study had extrapyramidal symptoms during post operative period, may be because of the use of single, minimal dose of Droperidol (Foldes et al, 1966).

Facial and Neck muscle rigidity was observed in 7.5% cases in both group A and C leading to difficult intubation. Tornetta in 1969 also reported acute rigidity
of facial, mandibular and pharyngeal muscles in immediate post Innovar injection period occasionallly interfering with ventilation. Janis (1972) observed sustained and rapid development of acute stiffness of neck and back muscles with facial grimace, chest wall rigidity or ventilatory impairment following intravenous Innovar injection in premedication.

Awareness during anaesthesia was another drawback of this technique found in our study. The incidence of awareness was maximum in group B (52.8%) while it was 5% and 10% in group A and C respectively. This difference may be attributed to less sedative action of Pentazocine used as analgesic in group B. Presence of awareness may be attributed to insufficient intraoperative neurolepsis (Kreuscher, 1973) with use of lower doses of Droperidol (0.15 mg/kg).

In the postoperative period commonest complications were nausea, vomiting, hypotension, mental depression and apathy. None of the patients of our study had vomiting either during induction or in immediate recovery period. This could be attributed to antiemetic action of Droperidol confirming the views of Dobkin et al (1964) and Corssen et al (1964). However, nausea and vomiting occurred in 1st 24 hours during postoperative period. Vomiting occurred in 3 patients in group B and 1 patient each in group A and C. All of these
cases had undergone major intraabdominal surgery. The overall incidence of nausea and vomiting in the series of Holderness et al (1963) were 6.4% similarly Prys-Roberts and Kelman (1967) reported 4.4% incidence of nausea and vomiting with the use of Droperidol and Fentanyl. Iwatsuki et al (1971) reported 2.5% and 2.2% incidence of nausea and vomiting respectively in a series of cases who underwent surgery under modified method of neuroleptanaesthesia using Droperidol and Pentazocine.

Hypotension occurring in the postoperative period in 2.5% cases of group A and 2.5% of group C and were corrected effectively by fluid replacement. Thereby suggesting inadequate fluid replacement as the causative factor of hypotension.

None of the patients of this study had recurrent respiratory depression in postoperative period except that of in immediate recovery phase. This is because of shorter duration of action of Fentanyl, as also reported by Romagnali (1973). This shorter duration of action of Fentanyl after a single moderate dose is due to its rapid redistribution from brain to other tissues and that repeated or large doses leads to accumulation of Fentanyl and consequently ventilatory depression (Hug and Murphy, 1979).
Becker et al (1976) have reported prolong and recurrent ventilatory depression in patients who have been given Fentanyl during general anaesthesia.

Meclain and Hug (1974) suggested that Fentanyl accumulation may be associated with cumulative respiratory effects since there appears to be a close correlation between plasma level of Fentanyl and ventilatory depression in man.