REVIEW OF LITERATURE
Until the mid nineteenth century, relief of pain needed during surgery was achieved with natural substances such as alcohol, opium, hyoscine, cannabis indica and occasionally by concussion or suffocation. The problem of inducing quick, safe and easily reversible unconsciousness for any desired length of time in man only began to be solved in the 1840's when nitrous oxide, ether, and chloroform were introduced into clinical practice in rapid succession.

In 1920's ether and chloroform were the main anaesthetic agents used while nitrous oxide and ethyl chloride were often employed for induction. The open drop method was the most popular since the early Boyle's machine which first appeared in 1917, made slow progress.

The use of intravenous anaesthesia dates back to 1872 when Pierre-Cyprien ore used chloral hydrate intravenous hedonal was used in 1905 by Krawkow. Bredenfeld (1916) used intravenous morphine and hyoscine for 'twilight sleep'. Kirschner gave avertin intravenously in 1929. Hexobarbitone was the first drug to make intravenous anaesthesia popular after its use by Weese and Scharpf in 1932. Pentothal Sodium was synthesized by Tabern and Volwiler (1935) and introduced into clinical practice by Lundy of Mayo Clinic in 1935.


HISTORY OF NEUROLEPTANAESTHESIA:

In the above era of mononarcosis the principal requirements of an ideal anaesthetic state were provided by means of inhalation or intravenous anaesthetic drug. On the basis of Woodbridge's (1957) definition of this ideal anaesthetic state, surgical anaesthesia may be attained by providing adequate analgesia, hypnosis, muscle relaxation and protection from neurovegetative reflexes. Obtaining these several effects by means of single volatile or injectable drug could only be possible at the risk of immediate or secondary central or peripheral toxic effects.

So, to avoid these toxic phenomena as far as possible and to ensure the evaluation and control of each of the elements in surgical anaesthesia, the concept of 'potentialized' anaesthesia was brought into light first by combining the curare with the injectable barbiturates (Laborit, 1950 and Huguenard, 1950).

In 1953, DuCailar proposed large doses of ganglioplegics and antihistaminics to complement general anaesthesia, the so called lytic cocktail, to produce a state characterized by marked depression of reflexes and artificial hibernation. Severe fall in blood pressure and variation in individual ability to preserve the vegetative functions and circulatory stability
were instrumental in the failure of this polypharmacological method (Nilsson, 1963).

In 1959 De-Castro and Mundelee, for the first time proposed to the National French Congress of anaesthesiology the term NEUROLEPTANALGESIA. The goal of this method is to put into practice a more sensitive anaesthesia subtly adopted to each specific case and above all, less depressive and more protective than anaesthesia with a single drug. Neuroleptanalgesia by sparing many of the central nervous system structures and pathway usually blocked by so called orthodox anaesthesia, produces no hypnosis or muscle relaxation but provides intense analgesia and vegetative reflex blockade. This is beleived to result from thalamic analgesia and mental disconnection from the environment but with greater functional integrity of the autonomic centres remaining.

Since 1959 anaesthetists in continental Europe used various combinations of narcotic analgesics and butyrophenones intravenously for surgical anaesthesia (De-Castro and Mundelee, 1959, Nilsson and Janssen, 1961).

In 1963 Nilsson, proposed the concept of obtaining selective nervous system sedation and pain relief without the use of barbiturates or volatile inhalational anaesthetic agents by combining a morphomimetic and a neuroleptic drug.
Most anaesthesiologists have intended to regard this technique as a way to supplement established anaesthetic methods and become useful addition to the practice of balanced anaesthesia rather a new type of anaesthesia (Spoerel and Chan, 1965).

NLA-I REGIME:

Neuroleptanalgesia has been in clinical use since its introduction with Haloperidol and phenoperidine described as NLA formula-I. In Britain an early report (Brown and Horton, 1963) on its use with light general anaesthesia for neurosurgical procedures claimed that it constituted a major advance in anaesthesia for operations lasting longer than 1 hour. But its general spreading was hampered by the side effects appearing quite often namely, profound hypotension, extrapyrimidal disturbances and in a few instances prolonged post-operative psychic changes ranging from diminished power of concentration to hallucination which were mostly due to cumulation of the analgesic (phenoperidine) and neuroleptic (haloperidol) used. So this drug combination had not permitted to proceed with neuroleptanalgesia with an appropriate safety.

NLA-II REGIME:

Droperidol and Fentanyl, synthesized by Janssen and put on the market by chemical works of Godeon
Richter Ltd., were found practically free from the aforesaid disadvantages. Due to the harmlessness their large spectrum of efficiency and easiness of dosage these drugs are considered superior to NLA-Formula-I.

Patients who received Oxygen and nitrous oxide in addition to Droperidol and Fentanyl not only attain analgesia and sedation but also lose consciousness or in other words become anaesthetized. The term neuroleptanaesthesia was proposed by Foldes and associates in 1966 to characterize the state of these patients.

Neuroleptanaesthesia induced with a fixed 50:1 mixture of Droperidol and Fentanyl citrate, nitrous oxide and Oxygen rapidly became a widely used anaesthetic technique.

Holderness and Chase (1963) used dehydrobenzperidol and Phentanyl in 400 cases and found cardiovascular stability but have reported sharp fall of blood pressure in 1 patient and gradual fall of systolic blood pressure of approximately 25% of the preoperative level in 22 cases. Reduction in rate and depth of respiration occurred maximum during induction associated with rigidity of skeletal muscles in 8% of cases. Emergence from anaesthesia was smooth, consciousness and orientation returned soon after the discontinuance of nitrous oxide, post-operative nausea occurred in
23 patients and post-operative analgesic requirement was less.

Corssen, G (1966) used Innovar in doses of 1 ml per 10 lbs. of body weight in 510 poor risk patients and found it sufficient to induce and maintain anaesthesia for several hours. This general dose schedule was increased or decreased according to the anaesthetic risk. Besides apnoea or marked respiratory depression accompanied by chest wall rigidity other complications included transient hypotension (82 cases), extrapyramidal muscular twichings (5 cases), post-operative emesis (4 cases) and increased systolic and diastolic blood pressure (2 cases).

It seemed probable (Foldes et al, 1964) that the complications associated with neuroleptanaesthesia might be due to clinicians uncritical acceptance of the 50:1 fixed mixture of Droperidol and Fentanyl. This mixture was introduced into anaesthetic practice without the prior investigation of the pharmacological effects of its individual components in man. Consequently before attempting to develop a trouble free widely applicable technique of neuroleptanaesthesia it seemed essential to investigate the pharmacological effects of Droperidol and Fentanyl in human subjects.

The results of clinicopharmacological studies by Foldes et al (1966) indicates that the administration
of a fixed mixture of the slow acting and long lasting Droperidol and fast acting and short lasting Fentanyl, is pharmacologically unsound. It also becomes evident that the ventilatory difficulty encountered during anaesthesia were due to overdoses with Fentanyl and late extrapyramidal excitation observed after neuroleptanalgesia was probably caused by the unnecessarily large doses of Droperidol used. It was therefore decided (Foldes et al, 1966) to develop a technique of neuroleptanaesthesia based on the administration of a single dose (0.15 mg/kg) of Droperidol followed by intravenous injection of repeated small doses of Fentanyl which in conjunction with the nitrous oxide and oxygen would provide adequate anaesthesia without apnoea or undue depression of the respiratory rate. Muscle relaxants were to be used only for endotracheal intubation and to provide surgical relaxation without total paralysis of respiratory muscles. It was expected that by assisting spontaneous ventilation at the rate and rhythm determined by the patient and tidal volume by anaesthetist, ventilatory difficulty during anaesthesia could be prevented and by using only a single moderate dose of Droperidol, the post anaesthetic extrapyramidal excitation could be avoided.
Schotz and Zeigler (1967) used controlled technique with a dilute intravenous drip of Innovar to obtain a steady state in patient with high metabolic rate and increased tolerance and found reduction in total dose required as well as their disadvantages.

Foldes (1970) attempted to replace Droperidol with other ataractic drugs for example largactil, triflupromazine and hydroxyzine but were unsuccessful. However they could obtain satisfactory neuroleptanaesthesia with the use of meperidine, alphaprodine or morphine sulphate instead of Fentanyl employed in conjunction with Droperidol. Their study indicated that Fentanyl did not seem to offer any significant advantage over meperidine except for a lower incidence of apnoea and more rapid recovery of consciousness at the termination of anaesthesia.

Kay and coworkers (1970) recommended Pentazocine as a suitable alternative for Phenoperidine in combination with Droperidol in neuroleptanalgesia for neuroradiological procedures because of its fewer cardiovascular changes and less respiratory depression. Iwatsuki and associates (1971) had applied this modified method in more than 800 cases. The results were compared with those of original method using Droperidol and Fentanyl. This study indicated the usefulness of pentazocine as an analgesic component
in neuroleptanalgesia. The modified method using Droperidol and pentazocine produced smooth induction of anaesthesia, stable cardiovascular state during surgery, rapid recovery from anaesthesia and physical and mental quiteness in post-operative period with minimum incidence of nausea and vomiting. A lack of severe respiratory depression and ventilatory difficulty due to muscle rigidity was another advantage of this modified method over the original one. It is also convenient for clinical practice that the analgesic used is not a narcotic. However the respiratory depression produced by pentazocine can be easily antagonised by Doxapram (Yamato, 1973) without affecting its analgesic effect.

Foldes (1972) used Droperidol in combination with monoanaesthetic Ketamine to prevent or to diminish unpleasant dreams during recovery.

PHARMACOLOGICAL EFFECTS OF NEUROLEPTANALGESIC DRUGS

DROPERIDOL

Droperidol is a neuroleptic drug of the butyrophenone series which includes Haloperidol and Trifluperidol (Janssen P.A.J., 1966).

Chemical Formula : \( C_{22} H_{22} FN_3 O_2 = 379.42 \)

Chemical Name : 1-(1-3-(p-fluorobenzoyl)-1,2,3,6-tetra-hydro-4-pyridyl)-2-benzimidazoline.
DROPERIDOL
FIG. NO.-1

FENTANYL
FIG. NO.-2

PENTAZOCINE
FIG. NO.-3
Structural Formula: Figure No. 1

Signs of general anaesthesia:

Following intravenous administration of Droperidol there is a rapid induction of neuroleptic state. The term neurolepsis was first introduced by Delay and Deniker (1961), characterized by lack of initiative, disinterest in surroundings with conservation of conditioned response. Patients can be easily aroused and is obedient to commands.

The action starts within 2 to 3 minutes, is maximum after 10-12 minutes and persists for 6-8 hours (Janssen, 1966). It potentiates the effects of thiopentone. In association with thiopentone sleep time is doubled (Dobkin and associates, 1964).

Effect on component of neuron:

(a) Peripheral receptors: There is a weak antihistaminic action (Haase and Janssen, 1965).

(b) Afferent and efferent system: Extra-pyramidal seizures have been observed but these are relatively rare even when large doses are employed (Brown, 1964). Holderness and associates (1963) have observed extrapyramidal tract reaction such as oculogyric crisis in infants and children following a single dose of 1.2 mg per 10 lbs. of body
weight. This occurred after the sedative effect had disappeared usually 12-18 hours after injection. Corssen et al (1964) observed muscle jerking and twitching in three patients shortly after injection of Innovar. Tornetta et al (1969) reported 17 patients in whom acute rigidity of facial, mandibular and pharyngeal muscles, developed in the immediate post Innovar injection period, occasionally interfering with ventilation. Janis (1972) reported sustained and rapid development of an acute severe stiffness of neck and back muscles with facial grimace without chest wall rigidity or ventilatory impairment following premedication with Innovar intravenously. Most extra-pyramidal reactions caused by Droperidol are of dyskinetic type usually occurs in recovery period. These extra-pyramidal tract reactions tend to disappear following administration of benztropine or atropine (Patton, 1975).

**Effect on autonomic nervous system:**

There is an adrenergic blockade with a resulting decrease in peripheral resistance. Droperidol minimizes the rise in blood pressure caused by intravenous epinephrine and non-epinephrine (Holderness and
associates, 1963). In addition, Droperidol prevented ventricular arrhythmia induced by epinephrine given intravenously in dogs anaesthetized with pentobarbital. This blocking effect is due to an unclassical alpha-blocking action effecting epinephrine (Janssen et al, 1963; Schaper et al, 1963; Yelosky et al, 1963; Whitwam and Russell, 1971). Droperidol offers protection from surgical stress (Ferrari and Stephen, 1966) and provides optimal tissue perfusion (Corssen, 1966) by selectively blocking the alpha-receptors of the sympathetic nervous system and therefore suppressing the vasoconstrictive action of Catecholamines. However, in the isolated rabbit ear artery, Droperidol was reported to cause a non-specific inhibition of vasoconstriction responses and its adrenergic blocking properties has been questioned (Puddy, 1971).

Greene (1972) reported that solvents and preservative used with droperidol are partly responsible for its alpha-adrenolytic action but again it was confirmed that Droperidol have alpha-adrenergic blocking property in isolated blood vessel of the dog (Muldoon et al, 1977).

Droperidol has been used as an antishock drug on the basis of there being 10% increase in epinephrine level associated with shock (Mc-Neil, 1963). Due to its alpha-receptor blocking and tissue perfusion
improving effects, the drug can be widely applied with good result in the complex attendance of shock conditions of various origin. Because of the demonstrable lack of increased skin temperature it was felt that the increased flow probably occurs in muscles or arterial venous shunts (Schaper, 1963). There is no anticholinergic effect (Haase and Janssen, 1965).

**Effect on respiration**:  

The effect of Droperidol on respiration is slight (Yelnosky et al, 1963 and Schaper et al, 1963) by increasing respiratory volume relatively high dosage of Droperidol improve effective ventilation and oxygen saturation. Prys-Roberts et al (1967) have shown that neuroleptics do not potentiate the ventilatory depression of analgesics used concurrently in neuroleptanaesthesia although the combination produces more sedation than either neuroleptic or analgesic agent when used alone.

**Effect on circulation**:  

The Cardiovascular system is stable with only a slight fall in blood pressure due to reduction in peripheral vascular resistance, secondary to alpha-adrenergic blockade and also to direct peripheral vaso-dialatation. Dobkin et al (1964) treated 16 healthy volunteers with a 10 ml combination of 1 mg ml⁻¹ Droperidol and 0.02 mg ml⁻¹ Fentanyl and found
that "in most subjects the cardiovascular system remained remarkably stable during the action of this agent". There is no direct myocardial depression (Corssen, 1964) and the cardiac output is increased (Haase and Jonsen, 1965).

MacDonald and colleagues (1966) have measured changes of cardiac output during neuroleptanalgesia but did not consider changes to be significant clinically. Serious circulatory disturbances were not found following pre-medication with neuroleptic drug other then pre-disposition towards postural hypotension (Prys-Roberts and Kelman, 1967).

Droperidol increases the heart rate, coronary blood flow and left ventricular Oxygen consumption, while mean aortic pressure is considerably reduced. These effects are due to a fall in systemic vascular resistance caused by partial blockade of adrenergic alpha-receptors. The increase in heart rate mainly accounts for the enhanced myocardial consumption of Oxygen after administration of Droperidol. Compared with this the rise in cardiac index that results from the increase in heart rate is only of minor importance for the elevated oxygen demand (Sonntag, 1973).

Brain circulation and metabolism:

Nilsson and Ingvar (1966) studied the cerebral
blood flow during neureleptanaesthesia in cats and reported that Droperidol causes an increase in cerebral blood flow up to 76% and it may induce epileptic seizures because of increase in cerebral metabolism secondary to increased blood flow. On the contrary, Michenfelder and Theye (1971) have reported that Droperidol does not significantly alter cerebral oxygen consumption but results in gradual decrease in cerebral blood flow to 60% of control due to increase in cerebrovascular resistance. Thus, cerebral blood flow although reduced is adequate to meet normal aerobic metabolic requirements in the presence of normal haemoglobin and oxygen level.

Effect on digestive tract:

Halpern and Ducrot (1946) observed a motor depression of the digestive tract following therapeutic doses of psycholeptic drugs. On the basis of these studies Bergmann (1965) suspected that dehydrobenzperidol would have an inhibitory effect on intestinal motility and he undertook extensive and precise studies which led to the conclusion that innovar has no appreciable effect on intestinal function.

Antiemetic action:

Dobkin et al (1964) found that "the absence of vomiting during recovery was outstanding". Aubry et al (1966), Vandewalle (1967) and Crul et al (1967) experienced antiemetic effects of Droperidol. After
endoscopies and various important surgical interventions performed in neuroleptanaesthesia they claimed less than 1% incidence of nausea and vomiting. The overall incidence of nausea and vomiting in the study of Prys-Roberts and Kelman (1967) on 230 patients anaesthetized with neuroleptanaesthesia was only 4.4% in fentanyl group providing marked antiemetic effect of butyrophenones. The potent antiemetic effect of Droperidol eliminates vomiting during induction and maintenance of anaesthesia (Corssen, 1966).

**Effect on Hepatic Function**: Tornetta and Boger (1964) observed its effect on the state of liver by the serial control of 13 liver function tests (serum bilirubin, prothrombin time, alkaline phosphatase, SGOT, SGPT, BSP retention and Serum cholesterol etc.) and reported no significant deviation.

**Action at Cellular Level**: The mode of action of neuroleptic drug is believed (Edmonds et al, 1970) to depend on their ability to form a monolayer on certain biological membranes which act as a lipid water interphase. In this way they decrease the permeability of membrane by reducing its surface tension in a manner similar to soap and detergents (Seeman and Bailly, 1963). The action is known to be specific for cell membrane in
central nervous system excited by dopamine, noradrenaline and 5 HT. The permeability of such post synaptic membrane is normally regulated by the competitive inhibition of glutamic acid by gamma amino-butyric acid (Janssen, 1965). There is structural similarity between GABA and neuroleptics, the basis of which is the basic nitrogen linkage to an S-shaped 4-carbon atom chain. Janssen (1967) has proposed that by occupying GABA receptors on the postsynaptic membrane the neuroleptic drug decreases synaptic transmission and lead to a build up of the transmitter in the intersynaptic cleft. Neuroleptics also inhibit the reuptake of dopamine and noradrenaline into the storage granules of the presynaptic terminals particularly when the concentration of these is increased following treatment with M.A.O. inhibitors (Roos, 1965; Janssen, 1967) but they do not influence the deletion of cerebral noradrenaline induced by reserpine. Recent evidence suggests that although there is a storage correlation between the inhibition of amine uptake and the inhibition of operant behaviour induced by neurolepts no casual relationship has been established between the two phenomena (Dresse, 1967).

Neuroleptic drugs have a predilection of certain areas of the brain known to be rich in dopaminergic synapses specially those of the C T zone of Borison
and Wang (1956) and the extrapyramidal-nigrostraitum system related to operant behaviour (Hillarp, Fuxe and Dahlstrom, 1966).

FENTANYL

Fentanyl is a potent analgesic drug of the 4-aminopiperidine series (Janssen, 1962). The product is available as citrate.

Chemical Formula : $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O} = 336.46$

Chemical Name : 1-(phenethyl-4-(N-proplonylanilino)
piperidine citrate.

Structural Formula : Figure No. 2

Signs of general anaesthesia:

It is 100 times more powerful than morphine
miligram for miligram (Yelnosky and Gardocki, 1963). There is peak intensity of action (analgesia, respiratory depression and tranquility), appearing sooner than most narcotic analgesics after intravenous or intramuscular injection. The onset of action is usually within 2-5 minutes (Holderness and associates, 1963; Dobkin and coworkers, 1964), the duration of action is 30-45 minutes. The duration of respiratory depression is also less than most narcotic analgesics. Both the rate and depth of respiration may decrease, apnoea may appear. Its potency is 350-1000 times the potency of meperidine (Larson, 1963). All the action of fentanyl seem to be effectively antagonised by nalorphine or levallorphan (Foldes and others, 1965).
Effect on Component of Neurones:

Fentanyl depresses selectively the functional activity of those areas of brain stem which are concerned with a severe degree of respiratory depression. This respiratory depression is of such a nature that the automatic element of respiration fades out but the conscious patient nevertheless remains capable of breathing on command. This pharmacological effect is attributed to a gross or total loss of sensitivity to $\text{CO}_2$ in the respiratory centre. Despite this, function of reticular activating system is well preserved to maintain the consciousness (Hagoun, 1963).

Fentanyl blocks pain at the thalamic level with little effect on the cortex (McNeil, 1963), however work with stereotactic surgery has led to the observation that cortical stimulation of Brodmann's area causes a form of apnoea which can be corrected by asking the patients to breath. The same may occur with electrical stimulation of hippocampus (Dilagne, 1961).

Effect on autonomic nervous system:

Fentanyl has central vagal stimulant action which explains bradycardia and sweating (Holderness and coworkers, 1966). Both of which are reduced or eliminated by the preoperative administration of atropine in doses commonly used. There is no evidence of histamine release after Fentanyl (Dobkin and coworkers, 1965).
**Effect on Brain Circulation and metabolism:**

According to Brown (1964) Fentanyl does not produce cerebral vasodilation but it decreases the cerebral blood flow probably secondary to increase in cerebro-vascular resistance (Michenfelder and Theye, 1971).

**Effect on Respiration:**

Fentanyl produces marked respiratory depression. This effect appears in 5-10 minutes and lasts for 15-60 minutes after administration. The maximum peak effect is for 15-30 minutes. Both the rate and depth of respiration are decreased. Apnoea is shorter than the duration of analgesia (Nilsson, 1963; Dobkin and coworkers, 1964; Corssen and coworkers, 1964).

Profound ventilatory depression is a feature of narcotic analgesics which can not be separated from the analgesic action and may be manifested in number of ways. In conscious patients it causes a decrease in expiratory minute volume, rather than in the frequency of breathing (Jennett et al, 1968), since the changes are related to decrease in Oxygen consumption and CO₂ production.

The character of ventilatory depression was different when Fentanyl was administered to patients anaesthetized with 70% nitrous oxide and 30% oxygen (Prys-Roberts and Kelman, 1967). According to their
observations frequency of breathing is significantly reduced, minute volume and alveolar ventilation may fall despite a compensatory increase in tidal volume, thus alveolar Pco₂ tends to rise. The duration of raised PACo₂ is dose dependant and lasts for 15-30 minutes. Although the ventilatory depression occurring during neuroleptanaesthesia may be prolonged into the post anaesthetic period, the blood gas tension, acid base state after neuroleptanaesthesia do not differ significantly from those found after other anaesthetic techniques.

Although Fentanyl is considered to be a short acting narcotic analgesic (Romagnoli, 1973) but there are reports (Becker et al, 1976) of prolong and recurrent ventilatory depression in patients who have been given Fentanyl during general anaesthesia.

Studies in dog by Hug and Murphy (1979) suggest that the short 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. Later on Meclain and Hug (1979) 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. So the
anaesthesiologist should be aware of this potential for prolonged ventilatory depression from this short acting narcotic analgesic.

Respiratory depression is easily controllable. There is marked dissociation between the depression of respiratory and cortical areas, so that even apnoeic patients remain completely conscious and respond adequately to verbal instructions to breath (Corssen et al, 1964) controlled respiration provides effective ventilation, without loss of analgesia (Prys-Roberts et al, 1967).


Following a rapid intravenous injection of 0.1 mg of Fentanyl, there may be marked rigidity of the muscles of the arm, legs, abdomen and thorax which makes ventilation of the patients difficult (Holderness and coworker, 1963). Corssen (1966) however observed that "although this period does not last more than 3 to 5 minutes and subsides spontaneously it can be readily overcome by I/V administration of succinylcholine."

Kim Comstock et al (1979) studied the incidence of muscle rigidity and magnitude of hypercarbia during induction of Fentanyl - Oxygen anaesthesia, which showed high incidence of chest and abdominal wall rigidity and
inability to ventilate adequately thus resulting in progressive hypercarbia. Loss of consciousness and onset of muscle rigidity occurred at about the same time and dictated neuromuscular blockade in high percentage of patients in order to provide adequate ventilation.

There may be bronchoconstriction due to increased vagal tone (Holderness and coworker, 1963). If bronchoconstriction occurs the technique can be abandoned and anaesthesia can be continued with halothane or ether. If these are contraindicated, the bronchoconstriction can be treated by intravenous infusion of a dilute (1-2 mg per 100 ml) solution of isoproterenol hydrochloride (Foldes and others, 1966).

**Effect on Circulation**:

Fentanyl had been observed to cause hypotension (Larson, 1963; Gordocki and Yelnosky, 1964; Gorodetzky and Martin, 1965). It is generally considered to have very little influence on the heart and circulation (Shephard, 1965), apart from inducing a fall in systemic blood pressure which lasts for few minutes (Brown, 1965). However, the hypotensive effects of the drug following clinical dosage were not observed by Holderness, chase and Dripps (1963).

Mac Donald et al (1966) observed occurrence of raised cardiac output, central venous pressure and
mean arterial pressure simultaneously with an increase in FE'CO₂' which resemble the changes occurring with deliberate hypercapnoea during spontaneous ventilation rather than a direct effect of the analgesic drug. He has measured the changes of cardiac output during neuroleptanalgesia but did not consider the changes to be clinically significant.

By measuring the cardiac output and other haemodynamic variables Prys-Roberts and Kelman (1967) reached to the same conclusion as that of MacDonald, that is, cardiovascular effect of the analgesics were modified by alteration in ventilation, in particular with haemodynamic effects of concurrent hypercapnoea. Good cardiovascular stability after Fentanyl administration was also demonstrated by Tammisto et al (1970).

Robert K. Stoelting (1975) used high doses of Fentanyl with oxygen as an effective technique in patients with valvular and coronary artery disease undergoing elective open heart operation, since it minimizes alterations in cardiovascular dynamics. He noted increase in central venous pressure during drug infusion which decreased to awake level following controlled ventilation and skeletal muscle paralysis reflecting thoracoabdominal muscle rigidity rather than circulatory response. In patients with septic shock undergoing abdominal surgery, Stanley and
Reddy (1979) reported that large doses of fentanyl and oxygen produce complete anaesthesia but no cardiovascular depression.

**PENTAZOCINE**

Pentazocine is a benzomorphan derivative and a mild narcotic antagonist. It has recently been introduced as a potent analgesic. This drug is of great clinical interest because of the WHO's recommendations (1969) that at present it should not be subject to narcotic control. Since May, 1971, the drug is not under D.D.A. regulations.

Chemical name: \((1,2,3,4,5,6\text{-hexa hydro-3-(3-methyl-2 butenyl)-6,11-dimethyl-2,6-methano-3-benzazocin-8-01})\).

Pentazocine was synthesized at the Sterling Winthrop research institute in 1959. This compound was the result of search for a drug which did not have significant addictive potential and would be active when tested for its analgesic activity in man. This search gained momentum in 1954 as a result of report by Lasagna and Beecher, who observed that the potent narcotic antagonist nalorphine was equally potent analgesic as morphine. This observation was later confirmed by Keats and Telford (1957). While nalorphine appeared to be devoid of the addictive potential which exists for the narcotics, its dysphoric and
psychotomimetic effects inhibited its use as an analgesic. So the search continued for the compound which had weak narcotic antagonist activity in laboratory animals retaining potent analgesic action in man and devoid of addictive potential. Pentazocine appears to be the right drug fulfilling all the ideal requirements.

Pentazocine can be useful supplement to nitrous oxide-oxygen anaesthesia and that general anaesthesia potentiate the respiratory depression produced by Pentazocine. The onset of analgesic action is approximately within 2-3 minutes when given intravenously and 15-20 minutes when given by intramuscular route. The action lasts for about 3 hours (Tammisto et al, 1970).

Relative potency of Pentazocine and other analgesics:

One of the earliest studies of the effect of Pentazocine on post-operative pain was that of Keats and Telford (1964) who reported that 10-20 mg/70kg body weight of Pentazocine given intramuscularly produced analgesia equivalent to 10 mg/70kg body weight of morphine.

In a study of 2190 post-operative patients Gordon and Moran (1965) found 30 mg Pentazocine to be equi-analgesic to 10 mg of morphine or 75 mg of meperidine but Guldmann (1969) on the contrary found that 20 mg of Pentazocine had better analgesic action than 100 mg of meperidine.
Plasma concentration of Pentazocine correlates well with the onset, duration and intensity of action. After intravenous injection the peak of the brain concentration occurred within 10 minutes, at the time of peak concentration 10% of injected dose was in the brain while the corresponding value at 60 minutes was 2% (Coroneos and colleagues, 1974).

**Effect on respiration:**

Pentazocine shares with other strong analgesic drugs in the tendency to depress respiration as measured by changes in minute volume, arterial carbon-dioxide tension and end tidal carbon-dioxide tension, steady state carbon-dioxide responses and rebreathing carbon-dioxide response curve, (Davie et al, 1970).

The respiratory effect of Pentazocine has been compared with Phenoperidine in healthy volunteers by Jennett, Barker and Forrest (1968) who found that both drugs in approximately equipotent doses (Pentazocine 20 mg, Phenoperidine 1.5 mg) produced similar increase in PACO₂ of the order of 5 mm of Hg. but relative absence of disturbance in breathing pattern by Pentazocine is a striking feature. Kay and coworkers (1970) observed that respiratory depression was more persistent and disturbing to the patient both subjectively and as reflected in whole body oxygen
consumption with phenoperidine than that produced by Pentazocine. They found fall in respiratory rate and arterial oxygen tension similar for both drugs but the increase in PaCO₂ greater and more persistent with Phenoperidine.

The respiratory depression can be significantly reversed by the nonspecific analeptics methylphenidate or Doxapram (Telford and Keats, 1965) and by potent narcotic antagonist nalaxone (Kallos and Smith, 1968).

Effect on cardiovascular system:

Pentazocine differs in its cardiovascular effects from the classical morphine pattern of hypotension and bradycardia. Most investigators (Sadove et al, 1964; Ahlgren and Stephen, 1966; Norris and Telfer, 1968) have observed a rise in blood pressure accompanied by a slight tachycardia in conscious patients after pentazocine. Although Keats and Telford (1964) only encountered hypertensive effect at high dose levels in conscious patients (2 mg/kg) as did Brown (1969). Potter and Payne (1970) observed a significant rise in mean arterial pressure of 9.5 ± 4.9 mm Hg with a dose level of 30 mg given intravenously to conscious adults. This hypertensive effect is unlikely to be related to hypercarbia since its onset was too rapid and similar rise had been recorded during ventilation when the Pco₂ was constant by Tammisto and others (1967).
Potter and Payne (1970) also observed a similar pressor response when Pentazocine was given intravenously during anaesthesia with nitrous oxide and halothane but in contrast to the effects on conscious patient the pressor response was preceded by a transient period of hypotension which was accompanied by a slight bradycardia that persisted into the pressor response.

Davie, scott and Stephen (1970) reported an early transient fall in cardiac output after Pentazocine in patients anaesthetized with halothane. Simultaneously there occurred a sharp sustained rise in central venous pressure followed by a slight rise in mean arterial pressure. The cause of this hypertensive effect whether increased peripheral resistance or increase cardiac output 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 coworker (1970) did not observed any systemic hypertensive response when they used Pentazocine in conjunction with Droperidol as a modified technique of neuroleptanalgesia, which they say might be due to alpha-receptor blockade produced by Droperidol, confirming the views of previous investigators (Tammisto and colleagues, 1970) of the direct action of the drug on the arterial blood vessel. Any vasoconstriction of the pulmonary artery tree which
may possibly occur following Pentazocine would also be
blocked since MacDonald and associate (1966) recorded
a fall in pulmonary artery pressure following injection
of Droperidol.

**Effect on other organs:**

Pentazocine seems not to have any deleterious
effect on the blood picture or liver functions (Flavell
Matts and others, 1969). Sigman and Elwood (1967) have
reported that intramuscular injection of 30 or 60 mg
of Pentazocine to normal subjects did not cause a
significant change in glomerular filtration rate but
both doses caused a decrease in effective renal plasma
flow.

**Side effects:**

The side effects of Pentazocine resemble those of
other narcotic analgesics and include nausea, vomiting,
drowsiness, dizziness, sweating, rarely euphoria and
headache (Keats and Telford, 1964). Occasionally
psychotomimetic reactions with hallucinations and
unpleasant dreams have been reported at high dose
levels by Hamilton et al (1967).

**Pharmacological effects of Narcotic antagonist**

**Specific antagonist - NALORPHINE:**

Nalorphine is a specific narcotic antagonist, was
first described in 1915 by Pohl. The clinical signific-
ance of its antagonistic effect was not explored until
1951 when Eckenhoff et al reported the use of nalorphine
as an antidote to morphine poisoning in man. Wikler and associates (1953) demonstrated that nalorphine precipitates acute abstinence syndrome in postaddicts who had received morphine, methadone or heroin for brief period.

Chemical Name: 4-allylnormorphine hydrobromide

Structural Formula: Figure No. 4

The most striking property of nalorphine is its marked ability to prevent or promptly abolish many of the actions of Morphine. Narcotic induced euphoria, analgesia, drowsiness, respiratory depression, muscle incordination, depression of polysynaptic reflexes, vomiting, defecation, bradycardia, hypothermia, suppression of ACTH release, antidiuresis, miosis, hyperglycaemia and gastrointestinal spasm are all antagonised. Within 1-2 minutes after intravenous injection of 5-10 mg of nalorphine, there is prompt increase in respiratory minute volume, and PCO₂ decreases towards normal. If blood pressure is decreased, it tends to return towards normal. Antagonism of narcotic induced respiratory depression usually lasts for 1-4 hours (Woods, 1956).

Non specific antagonist – DOXAPRAM:

The doxapram an analept, introduced by Lunsford et al (1962) is reported to reverse post-operative hypoxia and hypercapnia. It is advocated for the therapy of respiratory failure resulting from chronic pulmonary disease where oxygen therapy may be expected to
NALORPHINE

FIG. NO.- 4

DOXAPRAM

FIG. NO.- 5
exaggerate hypercapnia and acidosis (Winnie et al, 1971). Unlike other analeptic agents Doxapram has a large margin of safety, the therapeutic ratio (Convulsive dose upon ventilatory stimulating dose) is about 20-40, compared with 2-4 for other analeptic agents suggesting that doxapram has a direct selective stimulatory effect on respiratory neurons at doses that do not stimulate nonrespiratory units (Funderburk et al, 1966). But Wang and Hirsh (1973) have suggested that the primary site of action of doxapram is on carotid chemoreceptors whereas Scott, Whitwam and Chakrabarti (1977) said that Doxapram produces respiratory stimulation mediated through the peripheral carotid chemoreceptors and as the dose level is increased, the respiratory centre in the medulla is stimulated with progressive stimulation of other parts of the brain and spinal cord.

Chemical Name: 1 ethyl-4-(2-(4 morpholinyl) ethyl)-3,3-diphenyl-2-pyrrolidinone hydrochloride.

Structural Formula: Figure No. 5

The onset of respiratory stimulation following the recommended single intravenous injection usually occurs in 20-40 seconds with the peak effect at 1-2 minutes. The duration of effect may vary from 5-12 minutes (Gupta and Dundee, 1974). The respiratory stimulant action is manifested by an increase in tidal volume associated with a slight increase in respiratory rate.
Doxapram counteracts the respiratory depressant effect of morphine without abolishing analgesic effect. Since it is quickly metabolized the effect is short lived so the immediate post operative period is crucial to the latter development of chest problem (Gawley et al, 1976).

Sakuraya and Fujita (1974) noted the ionotropic effect of Doxapram hydrochloride on cardiac performance when given during emergence from neuroleptanaesthesia confirming the finding of Wushima and coworkers (1974) who observed increase in heart rate and systolic and diastolic blood pressures when Doxapram was injected during the recovery period. They also found significant increase in tidal volume but not in respiratory rate. There was increase in $P_{aO_2}$ and fall in $P_{aCO_2}$ resulting in shift of blood pH towards alkalosis. The side effects of Doxapram viz. diaphorism and dyspnoea were observed in few cases when the drug was administered rapidly in patients who had laparotomy under neuroleptanaesthesia with Droperidol, Pentazocine and Nitrous Oxide.