Pain is one of man's most compelling experience. It is an unpleasant sensation frequently associated with physical damage, therefore often described by the patients in connection with injury. Sherrington (1906), in his classical work on the central nervous system has defined pain as, "the psychical adjunct to an imperative protective reflex". This concept draws attention to the protective aspect of pain in preventing body injury from noxious stimuli. It is considered a signal from a warning device, but, like other expressions of the regulatory mechanisms within the body, it sometimes, functions in an unsatisfactory way. It is not only a distressing experience, but if continued, it may have harmful effects on the vital organs leading to impairment of function or even tissue damage (Wolff and Wolf, 1958).

The persistence of pain may interfere with the surgical procedures and make them very distressing for the patient and also more difficult for the surgeon. Hence its alleviation during surgery is, therefore, the raison d'être of anaesthesia.

The endeavour of modern anaesthesiology stems around the attainment of ideal operating conditions (Co-operative and painfree patient) with the total body physiology maintained as near normal as possible. In order to hit the bull's eye, anaesthesiology today, is
armed with a number of drugs and techniques, which have some thing or other to boast their supremacy over the others, but still the eye could not be perforated.

General anaesthesia, although the most effective method of pain relief, is not without the risk of alterations in the cardiovascular and respiratory functioning, as also a definite change in body chemistry. These changes may not be of significance in normal patients but may have vital role to play in increasing the post-operative morbidity and mortality, in patients with metabolic and systemic disorders. With the suppression of reflexes the possibility of regurgitation and aspiration, under general anaesthesia, is also enhanced, particularly in patients with full stomach undergoing emergency surgery.

The absence of these limiting factors add a feather to the cap of local anaesthesia, thereby increasing its popularity under such circumstances. The discovery of a number of safe and potent local analgesic drugs, along with the evolution of various simple techniques of field blocks, has made them still more acceptable to the population as such.

One such technique, INTRAVENOUS REGIONAL ANALGESIA is a simple, effective, cheap and safe method of pain relief during surgery over limbs and can be repeated again and again. It claims special preference in busy hospitals and over worked emergencies where availability
of beds is a problem and rapid turnover of the patients, a must. Moreover most of the patients requiring emergency surgical intervention are not suitably prepared for an early general anaesthesia.

Almost a century has elapsed since local analgesic drug was injected intravenously by August Bier (1906) in 134 cases with no adverse effects. Several series were thereafter reported, but the technique got little attention. The credit for reintroducing intravenous regional analgesia in clinical practice goes to Holmes (1963), who suggested that lignocaine acted upon the motor and sensory nerve endings. He was ably supported by the studies of several workers, (Miles et al, 1964; Fleming et al, 1966, and Adriani, 1968). On the other hand Sorbie and Chacha (1965), concluded, on clinical and electrophysiological grounds, that the local anaesthetic acted mainly on the nerve trunks.

Various local analgesic drugs have been employed in this technique viz chloroprocaine, Lidocaine, Prilocaine and Bupivacaine etc, but an agent of choice which should provide wide margin of safety, rapid onset and longer duration of action is still at large. The occurrence of thrombophlebitis in subjects receiving chloroprocaine may be due to its acidity and contraindicates its use. Prilocaine is less likely to produce signs of central nervous system toxicity than lidocaine and is equally
as effective as lidocaine but however it has the
disadvantage of producing methaemoglobinemia.
Lidocaine is to be used with caution to avoid
sensitivity reactions. Bupivacaine takes its own
time to give full effect. Hence it can well be seen
that every drug has one or the other limiting factor.
Therefore under these circumstances the local
analgesic, CENTBCRIDINE, discovered at C.D.R.I.
Lucknow, is employed in this technique to establish
whether the drug is superior or not to the present
conventional local analgesic drugs.
REVIEW OF LITERATURE
The evolution of human race, although one of nature’s most beautiful gift to the world, carries along with it one of its most dreadful curses and that is pain. Man is born in pain, lives in pain and dies in pain, it is therefore an experience never welcome. Since time immemorial, man has been fighting against it but, has not as yet been able to give it even a proper definition, what to talk of conquering it.

Pain has mostly been defined in the past in connection with its protective aspect in preventing the body injury by noxious stimuli. Leriche (1949) has stressed that on many occasions pain seems pointless and quite often the warning it affords is inadequate. As a symptom pain demands instant relief and is present in two out of every three patients seeking medical advice (Devine and Merskey, 1965).

The history of pain relief dates back to first recorded evidence of human civilisation, but enormous development of surgery during the nineteenth and twentieth centuries could well be possible as a result of commendable advancements, made by the anaesthesiologists in the field of pain relief.

Anaesthesia today, can broadly be classified as general and local anaesthesia. With regards to local
anaesthesia, endeavours have been made for a long time, but the major problems have largely been overcome comparatively recently. Much work is still being performed and more so required to improve the situation.

Modern local analgesia began with the introduction of cocaine in 1884 by Koller. Substitutes for the toxic cocaine soon came into being. Giesel's tropocaine appeared in 1891, Einhorn's novocaine (procaine) in 1899, Fourneau's stovaine in 1904. Meischer and Uhlmann introduced nupercaine in 1929, where as amethocaine appeared in 1931. The most commonly used local analgesic drug of the present day, lignocaine, was gifted by Lofgren and Lundquist to our profession in the year of 1943, but was put in clinical use by Cordh in 1945. Amongst the more recent local analgesic drugs, bupivacaine came into being in 1963 (Telivuo), while mepivacaine was synthesized in 1956 (Ekenstam and Egner).

Centbucridine is a new local analgesic drug, synthesized at C.D.R.I. Lucknow. Indian contribution to the family of currently available local analgesic drugs.

The first available account of intravenous administration of local analgesic is by Alms in 1886 (cited by Adams, 1944), who has shown that the intravenous injection of a local analgesic agent was associated with analgesia in the area supplied by that gessel, later
the method was applied to man by Oppel and Goyanes (Allen 1914) and by Ransohoff (1910). The method is even occasionally mentioned today (Gevorkian 1962). But this knowledge was not put to practical use until, Bier (1908), published his account of venous anaesthesia for limb surgery. He had successfully given venous anaesthesia in about 30 cases. Many reports soon followed, Catz 1909, Hartel 1909, Hitzrot 1909 and Page & Mac donald 1909.

Bier's technique was described in detail by Adams, 1944. Bier's technique though effective was cumbersome. An improvement in the form of a single tourniquet method was described by Morrison (1931). The subject was well reviewed by Adams (1944), but the credit for the reintroduction of the technique goes to Holmes (1963). His series consisted chiefly of relatively short operative procedures of a type suitable for the casualty department.

PREMEDICATION:

Holmes (1963) believed that heavy premedication is beneficial. On the other hand, (Cox, J.M.R. (1964), had the opinion that for out patients, the distinct advantage of rapid recovery should not be offset by heavy premedication, Sadove, et al.,(1952), were of the opinion that sedation usually by barbiturates render the patients non-cooperative and the elicitation of analgesia becomes difficult. Moreover the cerebral cortex gets depressed and thus acts synergistically with lignocaine which also
depresses the brain.

TOURNIQUETS:-

An improvement in the form of single tourniquet was described by Morrison, 1931. Bell, et al, (1963), and Adams et al, (1964), have advocated the use of two tourniquet. Hoyle, J.R.(1965), introduced the use of two balloon cuffs. The upper balloon was inflated when the injection was being given while the second balloon inflated when the operation started. In this way tourniquet pain was abolished.

VENEPUNCTURE:-

Originally Bier had practiced cut down for the administration of drug and Morrison (1931) was first who suggested venepuncture and had made the technique more practicable. Holmes (1963), suggested that the site of injection whereever suitable, can be chosen distal to the tourniquet while Dawkins, et al,(1964), believed that it should be as near as possible, to the region of operation. Sorbie and Chacha (1965), were of the opinion that it should be in the distal part of the limb i.e. near or distal to the wrist or ankle because valves in the proximal part of the veins are very powerful and withstand considerable pressure, so that the downward flow of solution is slow and incomplete. Sorbie and Chacha, found that the time taken by the drug to spread after a proximal injection was longer than after a
distal injection. Time of spread to the whole limb after a proximal injection was 5 minutes and 40 seconds, whereas it was 4 minutes and 50 seconds after distal injection. The site should not be very close to the tourniquet to avoid toxic reactions, as syringe pressure may exceed 300 torr and analgesic solution can enter the systemic circulation from below the inflated tourniquet. (P. Prithvi Raj, et al, 1972).

**Exsanguination:**

Adams, et al, (1964), believed that exsanguination was of great importance for two reasons. Firstly the analgesic solution will be evenly distributed in the empty venous plexus and will also not be diluted by the blood present in the limb. Average blood volume in upper limb distal to the point of placement of the tourniquet was measured by Adams and Albert (1952), as 170ml. The concentration of 40 ml. lignocaine solution is much greater when 170 ml. of the blood is removed by elimination of this large dilution factor, as a result the analgesia would be even, complete and more prolonged. Secondly at the release of tourniquet there is no reservoir of blood containing drug ready to be dumped into the general circulation which may explain the lack of side effects in central nervous system as well as low blood levels of the drug determined chemically.

Exsanguination can be done by application of Esmarch's
bandage from fingers or toes upwards to reach the tourniquet (Holmes, 1963). But other authors (Dawkins, et al, 1964, and Cox, J.M.R., 1964), were of the opinion that gravitational drainage is good enough and there is no particular advantage claimed by using Esmarch's bandage and gravitational drainage is preferable where manipulation of the limb is painful. Holmes (1963), believed that the development of cutis marmorata leads to a reduction in the duration of anaesthesia. Bell, et al, (1963), concluded that the development of skin discoulouration was not associated with the degree and duration of analgesia, but with the appearence of these signs the operator is virtually sure of the success of technique.

Colbern, E.C. (1970), emphasises the necessity of exsanguination with the view that it produces collapse of the vascular compartment of the extremity. Injection of anaesthetic solution into a full vascular compartment will impair complete and even distribution throughout the extremity and with the tourniquet inflated the vascular compartment is a closed space and relative collapse of the compartment is necessary to accept the injected solution. He also suggested that desired result of exsanguination can be hastened by a careful milking of the limb, disturbing any painful lesion as little as possible. Pneumatic splint is also described as an another alternative for exsanguination. (Dunbar, R.W., Captain, M.C., and Mazze, R.I., 1967).
DOSE AND CONCENTRATION OF SOLUTION:

Holmes (1963), advised the use of 200mgm of lignocaine solution for upper limb and up to 400 mgm for lower limb, in a concentration of .5%. Bell, et al, (1963), have found that with a dose of 3 mg/kg body weight mild neurological symptoms were present in half of their cases and that bradycardia and E.C.G. changes were often seen. These changes were not seen when the dose was reduced to half, but then analgesia was insufficient, unless limb ischaemia, produced by inflation of the tourniquet, was effected at least twenty minutes prior to the injection of drug. This modification would seem to make the method tedious and time consuming to the administrator and very unpleasant to the patient.

The use of dose as high as 300 mg of lignocaine solution in two cases is mentioned by Dawkins, et al, (1964). Adams, et al, used 40-50 ml of .5% solution i.e. 200 mg to 250 mg of the drug.

Kennedy, et al, (1965), advocated the use of an average of 132.5 mg of the lignocaine, with a maximum of 300 mg in .5% solution. Bromage and Robson,(1963), have defined the upper dose limit of lignocaine in healthy individuals, for the avoidance of toxicity, at .3/ml/lb body weight.

Dawkins, et al, (1964), have also used 20 ml. of 1% concentration instead of usual, .5% concentration.
Prilocaine is used in varying concentrations of .5% to 1% and dose ranging between 3 to 5 mg/kg. (Harris, W.H., 1969). However it is associated with the formation of methaemoglobinemia and its use is restricted.

Chloroprocaine was used in doses ranging from 1 to 3 mg/kg in concentration of .25% to 1% with good results in 29 out of 38 volunteers. The incidence of thrombophlebitis was 6% in the series (Harris, W.H., Slater, E.M., 1965).

Bupivacaine was used by Moore, D.C. and Briddenbaugh, et al., (1971), for upper extremity in .25% concentration, using 30-50 ml of solution. Rausso, M, Drexler, H. and Aronson, H.B., (1981), have also employed bupivacaine in their series with this technique.

Suri, et al., (1983), are of the opinion that the effectiveness of the centucridine is dose/concentration dependant. Using 40 ml. of .35% solution they could produce consistent sensory and motor blockade with minimum side effects for surgical anaesthesia. A lower concentration (.25%) however was not sufficient while higher (.5%) concentration although produced good blockade and long duration of action, but was associated with several side effects.

DIXON's LAW :-

It states that the concentration of a local analgesic solution required to block the sympathetic fibres in a mixed nerve is lower than that for the sensory fibres and that again is lower than the concentration for the motor fibres.

The concentration spreads more
in inflamed tissues due to increased capillary permeability. The effect is more first on the nerve terminals of smaller diameters than sympathetic fibre and those conducting pain impulses.

MODE OF ACTION:

The mode of action of the intravenously injected local analgesic drugs still remains a ticklish problem. Various hypotheses have been put forward, but a concrete answer has yet to be achieved.

Bier (1903), used procaine hydrochloride with methylene blue into ischaemic limbs and noted the drug distribution in the tissues.

The drug diffuses slowly from the endothelium of the vessels into the tissues of the isolated limb. It is probably fixed to the nerve tissues and synapses and is stored in the tissue spaces. Not only the nerve trunk, but the nerve endings also get anaesthetised.

Distribution of the drug was studied by Shannon Cotev & Gordon, C, Robin, (1955), in dogs and Richard, E. Knapp and Myron Weinburg, (1959) by using lidocaine tagged with C$^{14}$ in adult monkeys. Levels of radioactivity after a determined time interval were obtained from specimen of extremity muscle, blood vessels and organs at autopsy. The anaesthetic solution was rapidly perfused throughout the tissues proximal to the site of injection and was held within the area bounded by
the tourniquet, until release. Within 30 minutes after release it was found throughout the body tissues. The concentrations of the anaesthetic solution present intravascularly within the anaesthetised fore limb, did not diminish significantly over a period of 90 minutes, and therefore release of the tourniquet may allow a significant concentrations of the drug to suddenly enter systemic circulation. Symptoms of systemic toxicity on tourniquet release are possible even after 90 minutes following injection of a local anaesthetic solution.

De-V-Van Niekerk a.d Coetzee (1955) used radio opaque material to study the drug distribution. Flesing, S.A., Veiga. Fires, J.A. and Mc Cutchcan, R.M., (1955), used lignocaine containing hypaque and concluded that the drug acts at tissue level on the nerve endings. Both motor and sensory nerve conduction have been measured in clinical (Adams, Dealey, Kenmore and Miles, et al, 1964), and experimental (Kenmore, et al, 1964) in intravenous regional analgesia and they found that conduction speed decreased from fifty two to forty two meters per second.

Recently a study was done by Dave, V.B., Ghate, S.V. and Rao, B. Venu prasad (1978), using radiocontrast material and found greater localization of the anaesthetic agent in the traumatized tissue.

There is a selective pick up of lignocaine by nerve
tissues as compared to other soft tissues (Shamay, Cotev and Gordon C. Robin, 1966). C$^{14}$ labelled lignocaine was detected in axillary veins blood even before the release of the tourniquet. It is due to normal intraosseous blood flow.

The effect of centbucridine on neuromuscular transmission is as follows as reported in the experimental work at C.D.R.I. The sciatic nerve anterior tibialis muscle preparation in chloralosed cats was used for this purpose. There was no effect of lignocaine in doses of 10 mg/kg I.V. and of centbucridine in dose of 2.5 mcg/kg I.V. Closed intra arterial injection of 400 micrograms of centbucridine however produced 100% block, which developed slowly.

It is of interest to consider how analgesia and muscular paralysis occur, during intravenous regional analgesia. The paraesthesia suggests the possibility of a true nerve block, perhaps, produced by the perfusion of the veins of the nerves. The rapid onset and recovery however point to a more peripheral site of action, such as at the nerve endings. Obstruction or extensive destruction of venous system will prevent the development of satisfactory peripheral anaesthesia. The safety of the technique probably depends on the fixation of a major portion of the anaesthetic agent by the tissues. The amount of the drug fixed is higher when
exsanguination is efficient. Dispersion of the anaesthetic solution is most rapid and complete when a hand vein is used for injection then where a cubital vein is chosen as the retrograde flow of the solution is prevented by the competent valves. (Sorbie and Chachra, 1965).

Prithvi Raj, P., Garcia, C.E., Burleson, J.W. (1972) concluded in their work that lignocaine acts at the main nerve trunk to produce clinical anaesthesia after intravenous administration.

ANOXIA:-

Anoxia is also held responsible for the production of anaesthesia by lowering the $p^H$ in the limb and increased $PCO_2$ both of which are known to modify the membrane permeability or the low $p^H$ expediting or increasing the ionisation of lignocaine or through accumulation of metabolites e.g. lactic acid or by the direct compression of the nerve itself. In whatever way the occlusion and anoxia act, it was observed that once the anaesthesia had set in it lasted for considerable time, but the tourniquet starts producing discomfort after 40-50 minutes, in some cases. With this technique ischaemia may contribute to anaesthesia when 30 minutes have elapsed after application of the tourniquet. Anaesthesia of a limb from ischaemia alone has a different pattern of onset to that following drug injection and is considerably slower in development. When arm subjected to
total ischaemia, anaesthesia is not complete for 40 minutes. Sensation is first lost from finger tips and gradually the anaesthetic area extends more or less evenly up the arm. Motor power is lost in a similar way. Extensors being effected sooner than flexors, there is a difference in the pattern of nerve conduction loss in the ischaemic limb as compared with the anaesthetic limb as shown in the nerve conduction studies which confirm that anaesthesia is not due to ischaemia alone. It is probable however that as time passes the anaesthetic solution leaks through osseous veins into general circulation and anaesthesia is maintained to some extent by the ischaemia (Sorbie and Chacha, 1965).

**PHARMACOKINETICS OF INTRAVENOUS REGIONAL ANALGESIA:**

The pharmacokinetic aspects of intravenous regional anaesthesia have been described by Tucker and Boas, 1971, they showed that after cuff release the peak plasma levels of lignocaine were 20 to 30 per cent lower than when the same dose of lignocaine was given by direct intravenous injection. The peak levels achieved were inversely proportional to the total time the tourniquet was applied and tended to be lower when the same dose was given by 0.5% rather than 1% solution. The release of lignocaine into the circulation was noted to be biphasic, with an initial fast release of about 30% of the dose, the remainder appearing by a gradual wash-out 50 percent of the dose of lignocaine can remain in the
arm 50 minutes after release of the cuff, so it is possible to re-establish anaesthesia within 10-30 minutes of the initial deflation of the tourniquet by reinflating and injecting half of the original dose of the drug.

**INJECTION Tourniquet RELEASE TIME INTERVAL:**

Toxic reactions appear to be more common when the injection and tourniquet release time interval is less than 25 minutes, as observed by Bier (1905), who advocated an interval of 30 minutes. He suggested that no matter how short the surgical procedure, the tourniquet should not be released before 20 minutes, at least. Morrison, (1931), after experimental work on cats, recommended that minimum interval between the injection of drug and release of tourniquet should be 30 minutes. Adams, et al, (1964), thought that the negligible toxic reactions in their series were due to the long interval of one hour. In the series of Dawkins, et al, (1964), the interval was as low as 10 minutes but the dosage was also high and as such it is difficult to say as to which of the two factors were responsible for the incidence of toxic reactions.

Kennedy, et al, (1974), stress the importance of 25 minutes of injection tourniquet release interval to prevent toxic reactions. The smaller the dose and greater the injection release interval, the chances of toxic reactions are less.
Edwin C. Colbern, (1970), suggests that tourniquet should not be deflated in a jerk, but it should be cycled to cut down on the bolus effect of the anaesthetic agent, as it is released into the general circulation. This is done by deflating the cuff for about 5 seconds then reinflating for about 45 seconds. The cycle is repeated 4-5 times and then the tourniquet is removed. Martin, G. Schiller (1976) also recommended the same.

**EFFECT OF ANAESTHESIA:**

In a series of 30 cases conducted by Holmes (1965), there was complete analgesia in 21 cases. In 7 cases, patients noted some discomfort which was tolerable and two cases failed owing to bad technique. Seventeen patients were fully satisfied with the method declaring it preferable to general anaesthesia, 3 patients commented about minor discomfort though they still felt that method was satisfactory, whereas four patients thought that general anaesthesia could have been better.

In the series of Bell, et al., (1963), 24 out of 26 cases had excellent analgesia while 2 failed.

Colbern, Edwin C., (1970), had waiting period of 3-5 minutes in his series for complete analgesia and he proposed, should analgesia not be complete, a lesser dose of 5-10 ml. of normal saline solution be injected and this manoeuvre usually results in complete success as it forces further distribution of the anaesthetic agent.
Bell's classification of degree of analgesia is as follows:

**EXCELLENT:**

Loss of sensory, touch, pin prick and deep pressure, position sense, marked or total paralysis and no pain or discomfort from the operative procedure along with no tourniquet pain.

**GOOD:**

Complete loss of touch, pain and position sensation but retained sensory response to maximum pressure when applied to the finger nail or toenail, interpreted as burning. Slight or no tourniquet pain. And motor paralysis little or none, when present it appeared late during operation.

**FAIR:**

Incomplete anaesthesia, with mild pain or discomfort in reduction of a fracture. Severe or mild tourniquet pain. But no general anaesthesia was required.

**POOR:**

Failure of anaesthesia

Reaction to tourniquet have also been classified by Mittal, N.K., and Kackar, S.N., (1972) as-

**WELL TOLERATED:**

When patient was comfortable and quiet.

**TIGHTNESS:**

Patient felt tightness in the limb but no supplementation was needed.
MILD DISCOMFORT:

When patient complained of marked tightness, was restless but required no supplementation.

MARKED DISCOMFORT:

When the patient constantly complained of tightness and required supplementation.

Dawkins, et al, (1964), in their series of 514 cases found excellent analgesia in 95% of cases. There was moderate analgesia in 3.5% and in the remaining 1.5% cases there was failure of analgesia.

Adams, et al, (1964), in their series of 26 cases, conducted on upper limb exclusively, had complete analgesia in 25 cases.

Cox, J.M.R., (1964), reported complete analgesia in 35 patients in his series of 47 cases, moderate analgesia in 5 cases and poor response in 5 cases.

Kennedy, et al, (1955), gave intravenous regional analgesia to 77 patients and found complete analgesia in 75% and moderate in 12% cases. Poor in 10% and failed to achieve any analgesia in 3% of cases.

The most discouraging results were found in the work of Kennedy, et al, (1955), and the discredit to this technique was as a result of his observations.

Sorbie and Chachra (1965), in their work on 123 cases found excellent result in 118 cases, moderate in 5 and had failure in 10 cases.
TOXIC REACTIONS:

Sadove, et al, (1952), have classified toxic reactions to local analgesic drugs as in normal individuals into
a- Central effect.
b- Peripheral effect.

In the central effect the stimulation of cerebral cortex and medullary centres was followed by depression and in the peripheral effect cardiovascular and respiratory systems were involved.

Moore and Bridenbaugh, (1960), believe that the bradycardia, associated with overdosage of local analgesic drugs is secondary to an initial tachycardia and to be caused by myocardial oxygen lack. This sequence of pulse rate change was not seen nor was there any other suggestion of hypoxaemia (Kennedy, et al, 1965). The bradycardia encountered in 15% of cases was attributed to medullary centre stimulation. E.C.G. signs of deteriorating cardiac activity were seen in 30% of cases described by Foldes, et al, (1960), in which acute toxicity experiments with lignocaine were carried out. Similar observations were described by Steinhaus, (1957), and by Stewart, et al, (1963). In the above series a variety of E.C.G. changes including S.T. segment depression, atrial and ventricular asystoles, nodal rhythm and sinus bradycardia were associated with release of the tourniquet, as was a fall in the systemic blood pressure in over 20% of the cases studied.
There seems to be several factors involved in the appearance of the toxic effects after the release of tourniquet. It would seem clear that, the most important causal factor is the dosage of the local analgesic agent employed. The other major factor responsible for the occurrence of side effects with this technique, appears to be the injection tourniquet release interval. Sensitivity as opposed to overdosage is probably a very rare cause of toxicity manifestation which is encountered only with lignocaine.

Moore and Bridenbaugh, (1960), believed that, in less than 2% of cases, in which systemic symptoms arise after the administration of local analgesic drug, can a true allergy to the drug may be held responsible. de-Clive, Lowe., et al, (1958), used lignocaine in supplemental form during general anaesthesia in many thousand patients without a single case of drug sensitivity.

In the study of Foldes, F.F., Robert Molly and Mc Nall, P.G., et al, (1960), Procaine hydrochloride, 2-Chloroprocaine 1 mg. , Lidocaine .5% and tetracaine hydrochloride, 0.125 mg. per kg. of body weight per minute were administered intravenously and chloroprocaine was shown to be the best tolerated and lidocaine the least well tolerated of the four compounds investigated.

Before this study the Centbucridine has not been used extensively as intravenous regional analgesic.
So reports on toxicity after intravenous route in human beings are available in only one series recently carried out by Suri, Y.V., Patnaik, G.K., Nayak, B.C., Gupta, P.P., et al. (1983), they found that cardiovascular stability was well maintained and there was no change in blood pressure or heart rate from the basal values after the release of tourniquet irrespective of the concentration or volume of centbucridine used. Cardiac rhythm was normal in all cases. Accidental deflation of cuff after administration of 40 ml. of 0.35% solution of centbucridine in one subject had produced moderate bradycardia. The incidence of other side effects like emesis, restlessness, facial flushing and venous thrombosis was highest in the group where .5% solution of centbucridine was used and lowest in the .25% group.

In the experimental studies after intravenous administration of small doses (5-80 microgram/kilogram) of centbucridine they had found a transient rise of 5 to 10% in blood pressure.

Liver has been shown to play an important role in the metabolism of lignocaine (Sung & Truant, 1954), and Geddes, (1958). Peak level of the drug is reached after the release of tourniquet. It may be a factor to be taken into consideration, where bilateral procedures are carried out. The additive effects of previous administration of drug, as shown by Bromage and Robson, (1961), would be considerably magnified when associated with hepatic insufficiency.
Release of metabolites including potassium may be a remote contributing factor for the causation of some of toxic effects associated with the release of tourniquet, (Kennedy, et al, (1965)).

The various types of toxic reactions encountered by different workers are depicted here as follows—Holmes (1963), in the series of his 30 cases, 5 patients complained of a sense of drifting away for a few seconds which was relieved spontaneously.

Bell, et al, ; in their series, on 26 cases, found giddiness, detachment, light headedness in 3 patients, and in another 4 cases he noticed cardiovascular disturbance in the form of wandering pacemaker and minor T, wave changes.

Dawkins, et al.; (1964); found nystagmus, ataxia and some times convulsions in 7 cases in the series of 514 patients.

Cox, J.M.R., (1964), reported twitchings, dizziness and paraesthesia in tongue in 5 out of 47 cases.

Maximum toxic reactions were reported by Kennedy, et al, (1965), drowsiness and unconsciousness in 7 cases, ventricular extra systole in 3 and cardiac arrest in one case.

DRUG:

Centbucridine is a 4-Nbutylamino 1,2,3,4, tetrahydrocridine hydrochloride, 4-N substituted 2,3-poly methylene quinoline (Patnaik, G.K., et al). International non-proprietary name of Centbucridine is BUCRICaine, given by , Geneva, Switzerland.
Photograph showing chemical structure of centbicridine
Its chemical structure closely resembles that of the previously existing local analgesic drugs like other local analgesic agents, it also has one hydrophilic amino group which is connected, by an intermediate chain to a lipophilic aromatic radical. Its structure is shown in the photograph.

Changes in any part of the molecule alter the anaesthetic potency and the toxicity of the compound, a fact that provides the basis for the vast number of available local anaesthetics.

Increasing the length of the alcohol group, leads to a greater anaesthetic potency. It also leads to an increase in toxicity so that compounds with an ethyl ester, such as procaine, exhibit the least toxicity. Length of the two terminal groups on the tertiary amino nitrogen is also important.

The structure of centucridine can be compared with the existing local analgesics, (Diagram).

**PHARMACOLOGY OF CENTUCRIDINE:**

It is a light yellow, crystalline compound of molecular weight 290.9. The melting point of the base is 65 °C and of its hydrochloride, 196 °C. The compound in solid state is stable for about 3½ years on storage at room temperature, while in aqueous solution (0.5% concentration) in an atmosphere of nitrogen it is stable for about 1½ years.

**LOCAL ANAESTHETIC ACTIVITY:**

It shows potent and reversible local anaesthetic
Structural Formulas of Local Anaesthetics
activity. This was evaluated by standard laboratory
tests, in the work done at C.D.R.I. Minimum effective
concentrations of centbucridine and lignocaine and the
duration of effect at these concentrations were determi-
ned as follows :-

A. **Surface Anaesthesia** (Rabbit cornea, Patnaik, G.K.,

<table>
<thead>
<tr>
<th>Centbucridine Lignocaine</th>
<th>Minimum effective concentration</th>
<th>Duration in minutes</th>
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<tbody>
<tr>
<td></td>
<td>0.2% 1.0%</td>
<td>15 15</td>
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B. **Infiltration Anaesthesia** (guinea pig intradermal
wheal method).

<table>
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<tr>
<th>Centbucridine Lignocaine</th>
<th>Minimum effective concentration</th>
<th>Duration in minutes</th>
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<tbody>
<tr>
<td></td>
<td>0.0125 0.1</td>
<td>25 20</td>
</tr>
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C. **Conduction block** (blockade of pressor response
to central sciatic stimulation in anaesthetised
cat by injection of 0.1 cc in the sheath of the
nerve proximal to the site of stimulation).

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<tr>
<th>Minimum effective concentration</th>
<th>Duration in minutes</th>
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</thead>
<tbody>
<tr>
<td>0.2 3.0</td>
<td>100 75</td>
</tr>
</tbody>
</table>

**POTENTIATION OF LOCAL ANAESTHETIC ACTIVITY BY EPINEPHRINE:**

As in the case of lignocaine, the local anaesthetic
activity of centbucridine is potentiated by epinephrine,
but a much smaller amount was required than generally
employed with lignocaine, however, there is a marked increase in the duration of anaesthesia.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Concentration</th>
<th>Anaesthesia</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>5 microgram/cc</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Centbucridine 0.01%</td>
<td>Mild</td>
<td>7'</td>
<td></td>
</tr>
<tr>
<td>Centbucridine +</td>
<td>5 microgram/cc</td>
<td>Complete</td>
<td>90'</td>
</tr>
</tbody>
</table>

**EFFECT ON NEUROMUSCULAR TRANSMISSION:**

The sciatic nerve anterior tibialis muscle preparation in chloralosed cats was used for this purpose. There was no effect of lignocaine in doses of 10 mg/kg I.V. and of centbucridine in doses of 2.5 mg/kg I.V. closed intraarterial injection of 400 microgram of centbucridine, however, produced a 100% block, which developed slowly, while lignocaine was without any effect up to 1 mg, when administered similarly.

**EFFECTS ON C.N.S.** (Patnaik, G.K. and Dhawan, B.N., 1982):

None up to 1/5th L.D. 50. Larger doses produced signs of C.N.S. stimulation like tachypnoea, hyperreflexia, preconvulsions and with toxic doses clonic convulsions preceded by death.

**EFFECT ON C.V.S. AND RESPIRATION:**

These were studied in cats anaesthetised with chloralose. Centbucridine up to a dose of 2.5 mg/kg I.V. produced a transient, mild, dose dependent hypertension and respiratory stimulation without any effect on nictitating
membrane. The responses to acetylcholine and epinephrine were unaffected but histamine depressor response was completely blocked by 2.5 mg/kg dose. It possesses mild CNS stimulant vasopressor, antihistaminic, spasmytic and anti-arrythmic activity.

**EFFECT ON ISOLATED GUINEA PIG HEART:**

Both centbucridine and lignocaine had a negative inotropic effect. The effect of 20 microgram centbucridine was approximately equivalent to 100 microgram lignocaine.

**TOXICITY STUDIES:**

**Acute toxicity:**

This was determined over 24 hrs period using 10 animals at each dose level. The LD50 values in various species are given below:

- Mice - 35 mg/kg ip (cf. lignocaine 150 mg/kg ip).
- Rats - 45 mg/kg sc.
- Monkey - 10.5 mg/kg sc.

**Sub-acute toxicity:**

This was evaluated at $\frac{1}{2}, 1/10, 1/25, 1/50$ and $1/100$ LD50 in monkeys. No toxic effects were noted in rats and guinea pigs, monkeys in the lower three doses.

**Neurotoxicity:**

Centbucridine (0.5 and 1%) marcaine (0.5%) and lignocaine (5%) were injected intrathecally twice a week in rabbits for two weeks and no gross or microscopic changes indicative of toxicity, were observed
in the spinal cord or nerves. (Gupta, P. P., Nityanand, S., et al., 1982).

Teratogenicity:

These tests were undertaken in mice (10 and 40 mg/mice) and rabbits (4 and 20 mg/rabbit). Centbucridine did not produce any foetal malformation in either species. (Sethi, N. and Mukherjee, S. K., 1982).