REVIEW OF LITERATURE
Anaesthesia was not known prior to 1846 although the anaesthetic properties of ether was already described by Faraday in 1818.

The use of ether in 1846 by W.T.G. Morton opened up a new era of painless surgery with the help of drugs (Price and Dripps 1965).

Before this event, chloroform was discovered in 1831 in United States France and Germany simultaneously but was successfully used as a general anaesthetic by James Young Simpson in 1841. After that throughout the most part of world it became the anaesthetic agent of choice. But due to outstanding demerits of chloroform anaesthesia, like, fall in blood pressure, cardiac arrest etc. it became less popularized and some workers termed it as a dangerous drug due to its delayed poisoning.

By 1894 ether gained popularity due to the introduction of open ether by Jafferson in 1872 and just after this in 1874 Clover introduce the gas ether sequences. But the open ether technique reaches America in 1895.
When the pure sample of cyclopropane was prepared and tested by Hewer and Hadfield in 1941, it proved to be more potent and suitable anaesthetic agent due to cheap cost noninflammability and little depressant action on respiration blood pressure and cardia output.

With the introduction of newer volatile anaesthetic agent and muscle relaxant popularity of cyclopropane declined.

Krantz and associate (1953) evaluated the anaesthetic properties of trifloroethylvinyl ether and used clinically in 1961. He found that this compound have a low blood solubility lack of irritant action and marked analgesic action while inflammability and respiratory depressant action were its drawback (Conway 1965).

Although this agent had broad usefulness as an inhalation anaesthetic, in cardiac surgery, neurosurgery, pediatric surgery and obstetric anaesthesia, but it became less popular due to almost simultaneous introduction of Halothane, which was synthesized in 1951 and examined by Suckling in 1951. It was a safer anaesthetic agent.
It became more popular due to the smooth and easy induction rapid recovery and absence of irritation and minimal nausea and vomiting and above all its noninflammability (Johnson 1956, Bryce Smith and Burns et al., 1957 and Abajian et al., 1959).

There was tremendous advancement in the field of anaesthesia with the discovery of muscle relaxant beside the inhalation agents.

Tubocurarine was the first neuromuscular blocking agent which was first time discovered by King in 1935 but it was clinically used in 1942 by Griffith and Johnson (Griffith H.R. and Johnson G.E. 1942).

This drug was first used for abdominal surgery as a muscle relaxant in 1946 by Harroun in Britain (Harroun P. et al., 1946) and was established by T.C. Gray and John Halton of Liverpool in great Britain (Gray T.C. 1946).

After the introduction and establishment of tubocurarine the pharmacologist throughout the world sought for synthetic drugs with a similar action and properties to that of tubocurarine.
As a result of this search gallamine triethiodide was synthesized and described by Bwvet in 1947 and used clinically by Huguennard and Bone in 1948, in France and by Mushin and his colleagues in England in 1949 (Mushin W.W. et al., 1949).

After this there was the chain of the various muscle relaxant come into light day by day.

In 1948 thonium was described by Barlow and Ings and it was clinically used by Organe in 1949 (Organe G.S.W. et al., 1949).

Danial Bovel and his coworker of Paris introduced two muscle relaxant one gallamine ethiodide in 1949 and other suxamethonium.

Suxamethonium was first used in anaesthesia by Von Daldel of Scottholm in 1951 and by Ottomeray Hoffer in Vienna and by Cyril Fredrich in Britain. Its effect in anaesthetized animal and man was described by Castillo and De Beer in 1950 and by Theself in 1951.

In 1947 Bovel and his coworkers described a synthatic muscle relaxant gallamine triethiodide. The effect of this relaxant in man was first described by Huguennard and Bone (1948) in France and by Mushin
and his colleagues (1949) in England.

Gallamine triethiodide is chemically tri
(B-diethylaminoethoxy) benzine triethiodide. It is
white amorphous powder, nonirritant relatively
stable and available in 40mg/ml solution in 2ml
and 10ml amples.

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\begin{align*}
& \text{C} - \text{C} \equiv \text{H}_2 - \text{C} \equiv \text{H}_2 \quad \text{N}^+ \text{[C} \equiv \text{H}_5] \text{J}^3 \\
& \text{C} - \text{C} \equiv \text{H}_2 - \text{C} \equiv \text{H}_2 \quad \text{N}^+ \text{[C} \equiv \text{H}_5] \text{J}^3 \\
& \text{C} - \text{C} \equiv \text{H}_2 - \text{C} \equiv \text{H}_2 \quad \text{N}^+ \text{[C} \equiv \text{H}_5] \text{J}^3
\end{align*}
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\underline{GALLAMINE TRIETHIODIDE}

The intravenous bolus dose of gallamine
triethiodide is most preferred route. The onset of
action occur within 90-120 second and duration of
action between 20-30 minutes. Supplementary doses
of gallamine 20-40mg are given as required.
Gallamine triethiodide acts at the neuromuscular junction by nondepolarization block. The currare molecule combine with the end plate receptors.

Gallamine distributed throughout the body and about 30-100% is excreted unchanged in urine within two hours (Mushin et al., 1949). Prolong paralysis may follow the use of gallamine in cases with poor renal function (Fairley 1950, Montgomery and Benett Jones 1956, Faldman and Levi 1963).

This is partly due to the loss of redistribution sites in the kidney and also due to the lack of alternative pathway of excretion for the drug (Faldman et al., 1969).

It is bound to serum albumine and the increase in potency by increasing the pH.

In 1956 W.D.M. Patton made distinction between the depolarizing and nondepolarizing muscle relaxant depending upon the mechanism of their neuromuscular blocking activity.

Pancuronium bromide was introduced in clinical anaesthesia by Baired and Reid in 1967. It is an odourless white crystalline powder, with a bitter test. It melts at 215°C with decomposition.
Chemically pancuronium bromide is a bisquaternary ammonium compound which is relatively stable and is supplied for clinical purpose in 2ml ample containing 2mg/ml.

\[ \text{PANCURONIUM BROMIDE} \]

The intravenous bolus of pancuronium is the most preferred route onset of paralysis occur within 2 to 3 minutes. The paralysis produced by pancuronium last for about 25 to 45 minutes and a satisfactory 'topping up dose' is about 1/5 to 1/10 of the original paralysis dose.
Pancuronium acts at the neuromuscular function in man by nondepolarization (Baired and Reid).

Pancuronium is believed to be excreted mainly unchanged in the urine but can be biodegraded to less active and inactive compound by metabolism up to 15% of injected dose of pancuronium may be recovered from urine as 3-hydrozy derivative. In the absence of renal excretion large amount of the drug can be recovered from the bile much in the form of steroid in which the 17 acetyele group has been hydrolysed to either the hydrogen or hydrozy derivative (Agoston, Kerston and Meifer 1973, Agoston et al., 1973, Somogyi Shanks and Triggs 1977).

Like all the muscle relaxants it is highly charged ion and is therefore unlikely to pass vital membrane easily. There is no evidence available in man that it is not believed to cross blood brain barrier. It has very little fat solubility.

There was no evidence suggested hystamine release after administration of pancuronium however allergic reaction have been reported (M.C. Dowel and Clark 1969, Nana et al., 1972).
Hugin and Kissling introduced Alcuronium in 1961 and Pancuronium was discovered clinically by Baird and Ried in 1967 but used in anaesthesia by Burkett W.R. et al., in 1968.

In 1979 Vecuronium was introduced by Durant et al., and was introduced in clinical use for the first time, by Crul and Booij of France in 1980 (Crul J.F. and Booij L.H.D. 1980).

_CHEMICAL FORMULA CF Vecuronium_
Vecuronium bromide was originally known by its research code ORG NC 45 and was developed by David Savage of organon Technika, laboratories (Savage et al., 1980). Vecuronium was developed by nonhormonal properties of steroid molecule, which is an androstanyl derivative of acetylecholine.

Vecuronium bromide is a buffered freeze dried powder, available as 4mg per ample with 1ml ample of water for injection as solvent.

The powder can be kept for 3 years provided they are stored in the dark at a temperature below 25°C. The trade name of Vecuronium, norcuron reflects the fact that 'nor' indicates that Vecuronium has exactly the same chemical structure as Pancuronium except for the absence of a methyle group. The missing methyl group is one which is attached to the quaternary nitrogen atom which is itself attached to the 'A' ring of the steroid nucleus.

Vecuronium is a monoquaternary homologue of Pancuronium, having negligible ganglion blocking and vagolytic properties (Agoston et al., 1980).
The maintainance dose of Vecuronium is 0.03 to 0.05 mg/kg body weight. The duration of effect is 10-20 minutes. However the larger dose of Vecuronium could lead to prolonged total duration of action. It is metabolized in the liver and mainly excreted in the bile, a small quantity is also excreted in the urine.

Neuromuscular effects of Vecuronium are potentiated by both respiratory and metabolic acidosis. The alkaline medium accelerate the decomposition of Vecuronium. The potentiating effect of hyperventilation on the duration of neuromuscular block are probably minimal in clinical practice.

Cumulative effects was not seen after repeated doses of Vecuronium. Vecuronium possesses an antimuscarinic action 1-3 times than Pancuronium.

As our country is a developing country so the ether is still in use along with several muscle relaxant due to the shortage of the sophisticated and costly instruments. As for as the safety of the patient is concerned with the use of these agents. Various experimental studies have been performed with a view to investigate the effect of anaesthesia on blood sugar and its mechanism because level of the blood sugar is the one
of the parameter for the safety of the patient.

This study perhaps, started with the experiment of Seeting in 1905 on the dog, in which there was rise in blood sugar level after introduction of diethyl ether and was confirmed by other workers.

That ether produces hyperglycaemia in animals is proved beyond doubt, but whether there is any significant effect in man is still debatable. Same is the state of other anaesthetic agents.

Before evaluating the changes in carbohydrate metabolism during anaesthesia, it will not be out of place to first consider some physiological aspect of carbohydrate metabolism.
PHYSIOLOGICAL ASPECTS OF BLOOD SUGAR

Glucose, the main conversion product of carbohydrate food, enters the blood from the intestine. Since it is a readily diffusible substance, is distributed fairly uniformly throughout the body fluid both extracellular and intracellular.

Glucose is metabolically inert and can not be utilized as such. Sugar is constantly added to blood and being utilized and stored. So maintenance of the blood sugar at a constant level is a balance between production and loss.

During the process of metabolism of glucose the source, storage and utilization of glucose come into play. Nervous influence, enzymatic action and hormonal involvement also have a significant role.

With a correct coordination between the different endocrine glands, several enzymes and hormones, blood sugar is maintained at constant level. The liver has an important role in this process.

Anatomically liver is the largest organ with numerous functions. Among the different functions during carbohydrate metabolism it plays two important roles—
1- By breaking down of glycogen it can liberate glucose into the circulating blood to maintain the blood sugar at its normal level.

2- It synthesize glycogen from glucose or other precursors and store it.

   The glucose of the body arises from several sources:

   1- The first is the intestinal absorption of the product of carbohydrate digestion.

   2- Next from glycogenolysis from glycogen by an initial phosphorolysis which gives Glucose-1-phosphate and this product in the body rapidly comes into equilibrium with its isomer Glucose-6phosphate to give glucose and is governed by enzyme present in the liver.

   3- Third source of glucose is from gluconeogenesis and the formation of glucose from noncarbohydrate precursors. Among these are glucogenic amino acids, glycerol and fatty acids arising from fats.

   As in the process of glycogenolysis the liver produces the necessary enzyme to hydrolyse Glucose-6-phosphate to yield glucose through gluconeogenesis.
Glucose absorbed from the gut is carried by the portal blood to the liver some of which is retained for conversion to glycogen. The reminder passes on to the systemic circulation for the use as follow.

1- It may be oxidised in the tissues.
2- It may be converted to fat.
3- It may be converted to glycogen in muscles, glycogen is formed in the liver. It consist of many hundreds glucose units linked together with the elimination of water. The formation of liver glycogen is summarised in fig.4

**PROPERTIES OF LIVER GLYCOGEN**

1. It is a suitable form to store carbohydrate.
2. Being insoluble it exerts no osmotic tension and so does not disturb the intracellular fluid content and does not diffuse from its storage site.
3. It has a higher energy level than a corresponding level of glucose.
4. It is the only readily available source for blood glucose.
5. It is radially broken down under the influence of enzyme into glucose in the liver and maintains a constant blood sugar level to produce energy.
A high glycogen content in the liver depresses the rate of deamination and leaves the aminoacids for protein synthesis in the tissues. Similarly a higher level of glycogen prevents the breakdown of proteins and prevents ketosis.

The quickest way of building of liver glycogen is by raising the blood sugar level rapidly by I/V injection of glucose.

**OXIDATION OF GLUCOSE AND GLYCOGEN IN THE TISSUES**

In some tissues glucose from the blood is utilized directly for the provision of energy eg. Nervous tissue which obtain their energy by direct oxidation of glucose. It dependent upon the adequate level of circulating blood glucose because they have very low glycogen reserve. When the glucose is used up for energy it is first broken-down to pyruvate in the process of glycolysis and the pyruvate is then oxidised to \( \text{CO}_2 \) and water in the citric acid cycle (fig. 5).

**CONVERSION TO FAT**

Conversion of sugar to fatty acids involves the breakdown of carbohydrate to pyruvic acid and then
Fig. 2 Sources of Glucose
Fig 3 SOURCES of GLUCOSE.
Fig 5
converted to acetylene CO-enzyme A. Molecules of CO-
enzyme A are condensed together to long fatty acid
chains which give rise to fat. This process is shown
in fig. 3

**MUSCLE GLYCOGEN**

This is formed from the circulating blood
glucose. The rate of formation of muscle glycogen is
increased by a rise of blood glucose and by the presence
of insulin. Muscle glycogen is consumed during exercise
and is built up again from glucose at rest. Muscle
glycogen can not be readily converted to blood glucose.

**BLOOD GLUCOSE REGULATION**

The normal morning fasting blood sugar level
in an adult varies from 80-120mg per 100ml of blood.
The concentration of glucose in human blood is the
same in the cells as that in the plasma.

The blood sugar level is maintained at fairly
constant level by a complex mechanism.

The main function of liver is building up and
breakdown of glycogen rather than its storage, in
carbohydrate metabolism. Under fasting condition when
sugar is not reaching the blood from the alimentary
canal the rate of glycogenolysis is equal to the rate
of blood sugar utilization and the blood sugar level is maintained relatively constant. At the same time gluconeogenesis start in the liver from noncarbohydrate material which make the hepatic glycogen store maintained when sugar is not available from G.I.T. The process of gluconeogenesis provides the liver glycogen from which the blood sugar is supplied.

In the muscle the blood sugar is built up into glycogen which gives rise to lactic acid and pyruvic acid during muscle contraction. Some of the lactic acid is diffused into the blood, reaches the liver and built up again into glycogen.

In absence of glucose supply from the gut the liver maintains the blood sugar. But when the supply from the gut is available the supply from the liver is temporarily cut off.

Insulin of pancreas controls the out put or intake of glucose by the liver in response to variations in blood glucose. Adrenaline on the other hand, by slowing the rate of formation of muscle glycogen from of blood glucose and introducing resistance to the migration of blood glucose to tissue causes hyperglycemia.
Insulin is essential for the maintenance of blood sugar and life is incomplete without it.

Glucose is inert unless it undergoes phosphorylation to Glucose-6-phosphate catabolized by the enzyme hexokinase. The insulin acts indirectly on hexokinase reaction.

In the anterior pituitary there is a specific inhibitor of hexokinase reaction when it is present in excess it slows the phosphorylation of Glucose-6-phosphate. Certain adrenocortical preparation prolong this inhibition.

An excess of insulin would overcome the physiologic inhibition of hexokinase reaction caused by the anterior pituitary inhibitor.

In presence of insulin, phosphorylation is accelerated and blood glucose level falls and all reactions of G-6-Po₄ would be accelerated eg. glycogenesis, lipogenesis etc.

Lack of supply of insulin or excess of anterior pituitary's inhibitor causes impairment of hexokinase reaction. In reverse conditions the utilization of glucose is slowed down and this leads to rise in blood glucose level. The combustion of blood glucose soon
increases and glucose is no longer available for energy. Tissue protein have to be drawn which result in fall of liver glycogen causing ketosis and negative balance takes place.

Adrenaline and noradrenaline raise the blood sugar level by stimulating glycogenolysis. This rise in blood sugar level ensures a supply of carbohydrate from the muscular activity of fight or flight which follows an initial stimulus.

Adrenaline stimulate glycogenolysis in both liver and muscle causing hyperglycemia thereby, a fall in liver glycogen. Administration of hydrocortisone cause a rise in blood sugar by stimulation of glycogenesis and to a diminished utilization of glucose.

Thyroid hormone has no role on blood sugar level.

There are many ways by which the nervous system brings about a rise in blood sugar:-

1. Stimulation through the hepatic nerves leading to the breakdown of glycogen already present in the liver.
2. Stimulation of internal secretion of adrenal gland.

3. Inhibition of internal secretion of insulin.

A much smaller quantity of adrenaline is required to raise the blood sugar.

When the requirements are more or less rate of production is regulated by alteration in the balance between the two antagonistic hormones, insulin and adrenaline in the blood. Adjustment in the balance between insulin and adrenaline is controlled by nerves.

As far as the effect of anaesthesia on blood sugar level is concerned various experimental studies have been performed. Seeling (1905) was perhaps the first person who has shown that the administration of ether in dog produces both hyperglycaemia and glycosuria by hampering with the action of insulin. However other anaesthetic agents did not interfere with insulin hyperglycaemia (Chamber's et al., 1927) or enhanced the effect of insulin (Aubertin and Tringuir 1932).

Thus the concept that anaesthetic might cause hyperglycemia by interfasting with the action of insulin in highly disputable.
Moreover ether did not produce its customary rise of blood sugar in patient with hepatic disease (Cantarow and Gerbert 1931). This finding together points to the role of liver in the hyperglycaemia of ether anaesthesia.

It is more probable that the rise in blood sugar is the result of increased hepatic glycogenolysis either due to direct action of ether or due to increased H-ion concentration associated with ether anaesthesia.

Some observers have recorded considerable increase in the blood sugar level sometimes more than 200mg% (Mehler 1927 Mackary 1928, Mackay and Dyke 1928 Minitts and Hupsers(1933) but Benerjee (1933) and Johnson (1949) have shown that this hyperglycaemia is the result of sympatheticoadrenal system with the subsequent release of epinephrine and mobilization of glycogen from the liver.

The demonstration of glucose intolerance during thiopentone anaesthesia appears to be relatively straight forward sympathoadrenal response. The blood sugar remains essentially unchanged in the fasting patient anaesthetized by thiopentone alone (Olmsted and Coulhard 1928 and Ravdin 1929).
Cantarrow and Gehert (1931) have studied the effect of ether anaesthesia on patients having liver and biliary diseases and found that glycogenic function of liver is impaired and the ether did not produce its costummary rise of blood sugar in such patients because it is fairly well established that anaesthetics diminished the uptake of glucose by the tissue (MacIntosh and Pratt 1938).

Knofel (1936) advance the theory that anaesthetic agents acting on the cerebral cortex causes hyperglycaemia by stimulating the sympathetic system and production of epinephrine as there is no rise in blood sugar level in cases of patients having bilateral adrenalectomy (Macraie 1931).

Thus the mechanism of producing hyperglycaemia appears to be due to a central stimulation which is transmitted to the adrenal gland through the sympathetic system and these glands by hormonal action cause glycogenolysis in liver. Later on Johnson (1949) also observed the same finding. The acceptable hypothesis which gain the strength that the anaesthetic agent bring about the release of adrenaline into blood stream from the suprarenal gland inturn accelerate the disintegration of liver glycogen and so mobilize glucose.
According to Engstrand and Friedberg (1945) parenchymatous organ especially the liver are injured under nacrosis during anaesthesia and this nacrosis causes the highest degree of hyperglycaemia due to overflow of the epinephrine from the adrenal gland.

MacIntosh and Pratt suggested that ether and other anaesthetic agents accelerate the breakdown of glycogen in the brain, liver muscle and other tissue of the body causing the increase the blood sugar level. According to these worker this is the compensatory mechanism means to minimize the effect of anoxia upon nervous tissue caused by anaesthetic.

Several procedure eg. high spinal anaesthesia above 4th thorasic segment (in which splenchnic nerve was blocked), denervation of adrenal, total sympathichtonary use adrenergic blocking agents have been shown to prevent hyperglycaemia due to ether nacrosis (Phillip and Freeman 1933, Johnson 1949).

Bunker (1958) stated that the most widly known clinical metabolic disturbance is the rise of blood sugar level during anaesthesia. While Murdoch (1958) said that anoxia itself causes most rapid rise in blood sugar level. Of the several hypothesis which is accepted
by many, is the hyperglycaemia occurring due to glycogenolysis in the liver as a result of liberation of catecholamine, particularly adrenaline, mainly from the suprarenal gland and also from the adrenergic nerve endings, due to the central activation of sympathetic system, caused by stress response during anaesthesia and surgery (Keating 1958, Annanumthodo Keating and Patrick 1958).

Haris (1959) has shown that with unpremedicated patients the induction of anaesthesia may cause considerable emotion and stress and consequently cause rise in blood sugar level. With this view Hunter (1959) carried out the experiment on blood sugar level and he concludes that during Halothane anaesthesia which is known to depress the sympathetic-adrenal system there was no significant rise in blood sugar level even after 2 hours (Topkins and Artusio 1959).

Brewster, Bunker and Beecher (1962) concluded that total pre ganglionic sympathetic block prevented epinephrine and nor epinephrine output during ether anaesthesia and the absence of metabolic acidosis and hyperglycaemia was due to the failure of catecholamine release.
The well known elevation of serum lactate and pyruvate and the less consistent elevation in citrate and alpha ketoglutarate which occur during ether anaesthesia but not with thiopentone may again be reasonably assumed to be related to increase sympathoadrenatine activity.

Irrespective of anaesthesia higher rise of blood sugar occurred in those patients who under went abdominal and pelvic operation than in those undergoing extra abdominal operation.

This might be due to handling of viscera which is known to cause sympathoadrenal stimulation (Griffith 1953).

Annamunthodo et al (1958) attributed the rise in blood sugar level to the mobilization of glucose from liver while Griffith (1939) has observed that rise in blood sugar level was proportioned to the blood level of adrenalin.

Clark (1968) showed rise in blood sugar during body surgery surgery with thiopentone nitrous oxide with or without relaxant. He observed that general anaesthesia itself did not show any elevation of blood sugar till the commencement of surgery and though that stress of
surgery increases circulating catecholamine and corticosteroid which in turn increase the blood sugar level.

Mehta and Buston (1975) postulated that surgical stress raises blood glucose which in turn is due to the activation of the hypothalamopituitary-adrenal axis and anaesthesia definitely modifies the effect of surgical stress.

The attenuation of blood glucose level changes varies with the anaesthetic technique (Amanunthodo et al., 1958, Browage et al., 1971 and Aheram and Walker 1979) depending upon their ability to suppress the reflex sympathetic activity in response to surgical stimulation.

Any form of stress is accompanied by change in the level of plasma cortisol catecholamine growth hormone, insulin and glucagon (Oyarma and Katsuki 1970).

The stress of surgical intervention has 3 component:-

1- The psychic stress due to fear of impending operation.
2- Stress due to anaesthesia.
3- Stress due to surgical trauma.
Preoperative psychic stress is reported to cause a significant elevation of blood sugar level regardless preoperative starvation (Allison et al., 1969).

R. Sudhina Laxmi, M. Usha Rani, D. Vijays Kumar Menon and M. Venketa Rao (1973) also observed in their work that there was a rise in blood sugar level after induction and during surgery. Ether showed hyperglycaemic tendency and maximum rise in blood sugar was observed in patients operated under ether anaesthesia.

As far as the effect of muscle relaxant is concerned its effect on blood sugar level during anaesthesia not much work have been done but it is clear that the muscle relaxant have no direct effect on the blood sugar physiology. Any change in the blood sugar level may be due to the other factors like anxiety, hypoventilation or hyperventilation during anaesthesia and lighter plain of anaesthesia.