REVIEW OF LITERATURE
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The function and life of cells depend upon the ability of the organism to produce and store chemical energy and its conversion to cellular work by the process of metabolism.

Anaesthesia is an induced state where the chemical anatomy within the living body is dismantled to a variable degree (Bose and Biswas, 1981). They also observed (1981) that carbohydrate and lipid metabolism are two pivotal components of the biochemical architecture, most vulnerable to affection in anaesthesia.

There is an increasing awareness that anaesthesia alone is not responsible for the metabolic changes, but surgical trauma also plays a role in the stress-response (Griffith 1953, Cullingford 1966 and Clark 1968, 70).

In order to understand and appreciate the complex stress response of the body to anaesthetic and surgical trauma, it is better to refresh our memory with a few glimpses at the human metabolism with an eye being kept on carbohydrate and lipid metabolism.

Intermittent dietary intake in presence of continuous utilization of nutrients by the tissues, makes it mandatory for the body to have a good reserve store of such nutrients. The total resources available to an average human (70 kg. body weight) are as follows:

Total calories = 126000 Kcal.

Daily dietary intake = 2% of above reserve.

A detailed table showing the full break-up of this reserve store is given on next page.
**Fuel reserves in a 70 kg. Man**

<table>
<thead>
<tr>
<th>Fuel</th>
<th>Tissue</th>
<th>Kcal.</th>
<th>Gm.</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglyceride</td>
<td>Adipose Tissue</td>
<td>100000</td>
<td>15000</td>
<td>80</td>
</tr>
<tr>
<td>Glycogen</td>
<td>Liver</td>
<td>200</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Muscle</td>
<td>400</td>
<td>120</td>
<td>1</td>
</tr>
<tr>
<td>Glucose</td>
<td>Body fluids</td>
<td>40</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Proteins</td>
<td>Muscle</td>
<td>25000</td>
<td>6000</td>
<td>19</td>
</tr>
</tbody>
</table>

(Plus 2% of this reserve as daily dietary intake = 2500 Kcal.)

*(Newsholme and Start, 1973)*

It is important that atleast one of these fuels is always available to the body. It is also imperative that the rate of production of each fuel be regulated precisely to the rate of its utilization and the rates of production and utilization of all fuels be integrated satisfactorily.

The metabolism of higher animals suffer from several disadvantages:

1. Some tissues (RBCs) are totally dependent while others (brain and renal cortex) are partially dependent upon glucose as the only metabolic fuel. Therefore adequate supply of glucose to such tissues must be maintained at all times.

2. The capacity of liver to store glucose as glycogen is limited, while adipose tissues store enormous quantity of triacylglycerol.

3. Higher animals are unable to synthesize glucose from fatty acids and therefore can not utilize this huge store of triacylglycerol, which does however contribute to glucose supply directly by providing
glycerol (a gluconeogenic precursor) and indirectly by providing fatty acids (FA) and ketone bodies (KB).

**INTERMEDIARY METABOLISM OF CARBOHYDRATES**

The chain of reactions that occur in body during the process of carbohydrate metabolism are as follow:-

1. **Glycogenesis** - It is the synthesis of glycogen from glucose to be stored in the body. Glucose is phosphorylated by hexokinase plus ATP to form glucose-6-phosphate (in the liver the enzyme is glucokinase). G-6-P is then converted to G-1-P under the influence of enzyme phosphoglucomutase. G-1-P reacts with uridine triphosphate (UTP) to form uridine diphosphate glucose (UDPG) which is converted by polymerization to glycogen under influence of enzyme glycogen synthase. The glycogen synthesis is promoted by insulin.

2. **Glycogonolysis** - Glycogen breakdown is brought about mainly in the liver to form glucose. The enzyme adenyl cyclase is first activated and catalyses the formation of cyclic AMP from ATP. This converts inactive phosphorylase to active phosphorylase which forms G-1-P from glycogen, the former being converted to G-6-P by phosphoglucomutase. G-6-Phosphatase converts G-6-P to glucose in liver (but not in the muscles) and promotes its entry in blood. Since muscles do not contain G-6-Phosphatase, G-6-P formed in the muscles enters either the Embden-Meyerhof or hexose monophosphate pathway to yield lactic acid as its final product.

3. **Glycolysis** - Oxidation of glucose or glycogen leads to formation of G-6-P which enters the Embden-Meyerhof pathway to yield the end products, lactate and pyruvate. The glycolysis is controlled by the rates of hexokinase and phosphofructokinase reactions (Lowry et al, 1964).
FIG. 6 - GENERAL OUTLINE OF THE OXIDATION OF GLUCOSE. 1. The absorption of glucose by cells, followed by the formation of glucose-6-phosphate, 2. the transformation of glucose-6-phosphate into 2 molecules of triose phosphates, 3. conversion of the triose phosphates into pyruvate, 4. the oxidation of pyruvate to acetyl CoA which is then oxidized by the TCA cycle.
4. **Tricarboxylic Acid Cycle** – Also known as Kreb's cycle or citric acid cycle. It is the final common pathway for oxidation of carbohydrate, lipid and protein. The pyruvate formed at the end of glycolysis converts to oxaloacetic acid which combines with acetyl CoA to yield citric acid, alpha-Ketoglutaric acid, succinic acid and finally oxaloacetic acid. In the whole process acetyl CoA is completely oxidized to carbon dioxide and water with liberation of energy at various stages in the form of ATP. The oxaloacetic acid reformed again enters the cycle by combining with another molecule of acetyl CoA.

5. **Hexose Monophosphate Shunt** – This is a direct oxidative pathway and serves as an alternative to Embden-Meyerhof pathway and Kreb's cycle. Here G-6-P is directly oxidized to carbon dioxide and water with liberation of energy.

6. **Gluconeogenesis** – It is the formation of glucose from non-carbohydrate substrates. According to Stanley (1981), It operates as:

   (i) By minimizing oxidation of glucose by recycling precursors (lactate) and via exchange reactions (alanine, glutamine).

   (ii) By de-novo synthesis.

   The lactate and alanine are converted into pyruvate, and glycerol into a triose-phosphate.

   Gluconeogenesis and glycolysis are the reverse processes and enzymes unique to either pathway, oppose those of other pathway at three sites.

   When liver glycogen stores are exhausted (starvation, stress), Gluconeogenesis is the only endogenous source of glucose
supply; the major sites being liver and renal cortex, while the major precursors are lactate (derived from anaerobic tissues e.g. RBC, renal medulla, testis, anaerobic respiration of glucose in muscles), glycerol (derived from lipolysis in adipose tissue), alanine and glutamine (derived from protein breakdown in muscles). Amongst amino acids, liver uses alanine while renal cortex utilizes glutamine. Efficient gluconeogenesis requires integrated metabolism of various tissues either supplying the precursors or producing glucose from these precursors. As the duration of stress (e.g. starvation) prolongs, the relative importance of liver as site of gluconeogenesis decreases, while that of renal cortex increases.

Gluconeogenesis from amino acids or glycerol represents a net gain of carbohydrate for the body, while that from lactate merely involves recycling of carbohydrate. The energy for this conversion is derived at the expense of fatty acids.

**BLOOD GLUCOSE REGULATION**

The blood glucose level at any moment represents an equilibrium between the rates at which glucose is entering or leaving the blood stream. Numerous factors contribute to the homeostatic processes which keep the blood glucose level constant within relatively narrow limits.

The final products of digestion pass through the portal vein to the liver where fructose and galactose are converted to glucose. Liver serves as a receiving, manufacturing, storing and distributing centre for glucose which is then carried in the blood stream to all parts of the body. The secretion of glucose from the liver tends to raise the blood glucose while its
Fig. 7 - Interconversion of glycogen and glucose-1-phosphate depends on the presence or absence of cyclic AMP. Without cAMP, the critical enzymes are in non-phosphorylated forms; glycogen synthase is independently active (solid arrow), while phosphorylase b is inactive (dashed arrow) unless a rise in 5' - AMP concentration signals a deficit of high energy phosphate.
Fig. 8 - The interconversion of fructose-1,6-diphosphate and glucose occurs by different routes in liver and muscle. Fructose diphosphate is converted to glucose in liver which diffuses into the blood.
removal by actively metabolizing tissues tend to lower it.

Liver cells are freely permeable to glucose, so the liver is capable of speedy responses to changes in blood glucose concentration. This, it self can determine whether the liver is a glucose-producing or glucose-using organ and at what rate glucose is taken up or released by this tissue (Soskin et al, 1938).

Enzyme glycogen synthase promotes conversion of glucose into glycogen, while glycogen phosphorylase and G-6-Phosphatase favour conversion of glycogen into glucose. The in-vivo equilibrium of these opposing enzymes is responsible for maintaining sufficient blood glucose concentration (Stalmans, 1976). Hepatic cellular responses to fluctuations in blood glucose level are also controlled by intermediary metabolites, ratios of oxidized to reduced co-enzymes, availability of ATP or ADP etc. These represent cellular processes independent of hormones. In addition, control by many hormones is superimposed on these more primitive control mechanisms.

Glucagon and beta-adrenergic agonists activate adenyly cyclase, thereby stimulating the cAMP dependent protein kinase which, in its turn, activates enzyme glycogen-phosphorylase and by resultant glycogen breakdown, raises the blood glucose level (Stanley, 1981).

Some other hormones (alpha-adrenergic agonists, vasopressin, oxytocin, angiotensin II) act in a different manner. They increase the level of mitochondrial calcium ions within liver cells with consequent stimulation of phosphorylase-β-kinase. The latter accelerates glycogen breakdown and increases glucose level in the blood (Stanley, 1981).

Insulin antagonises the action of all the above hormones. The mechanism of insulin action is not well understood, but one attractive possibility is that it stimulates one or more of the protein phosphatases
Factors which tend to raise blood glucose

Factors which tend to lower blood glucose

Hunger
Glucose absorption from G.I.T.
Hepatic Glycogenolysis
  a) Adrenaline
  b) Glucagon
Glucose diffusion in E.C.F.
Muscular exercise
Insulin 
Increased Glucose oxidation
Increased glycogen deposition
Increased lipogenesis
Decreased gluconeogenesis
Glycosuria (in diabetic patients)

Insulin destroying enzymes
MJ 1999 (by inhibiting adrenaline)

INTERMEDIARY METABOLISM OF LIPIDS

This consists mainly of metabolism of lipid storage site (i.e. adipose tissue), lipolysis, mobilization of fatty acids and their utilization.

1. **Adipose tissue and its metabolism:** Triglycerides account for about 90% of adipose tissue (Boyd and Lowe, 1957). This tissue is shown to metabolize glucose by the glycolytic, phosphogluconate and glucuronic acid pathways (Vaughen 1961, Winograd 1962), to carry out de-novo synthesis of FA and to synthesize triglycerides. These processes and their hormonal control represent an important regulatory component of
the overall carbohydrate and fat metabolism of the body.

Adipose tissue capillary endothelium liberates "lipoprotein lipase" which is responsible for release of free fatty acids (FFA) from circulating "glyceride lipoprotein complex". Insulin and dietary carbohydrates stimulate the activity of this enzyme. Additional lipase activity results in the breakdown of triglycerides (TG) to FFA and is influenced by a number of hormones. Adrenaline stimulates TG breakdown and release of glycerol and FFA (Hagen and Ball 1960, Winegrad 1962). Insulin increases FA and TG synthesis by possibly increasing the entry of glucose into the fat cell, which has very little capacity to phosphorylate glycerol and is dependent upon glycolytic production of glycerol phosphate for the formation of phosphatidic acids and TG.

Decreased glucose levels in muscle elicit an outflux of FFA from adipose tissue, which is carried to the tissues for energy production.

Uptake of blood glucose by the adipose tissue supplies acetyl CoA units for adipose lipogenesis. Adipose tissue contains an oxidative system that forms carbon dioxide and provides energy for FA and TG synthesis. Thus this tissue is a dynamic focal point of lipid metabolism.

2. Fatty acid mobilization: Following intracellular hydrolysis of triacylglycerol, FFA are released into blood. Due to relative insolubility, they are transported in the blood bound to albumin (and to high density-, low density-, and very low density lipoproteins).

Triglyceride lipase is the "flux-generating" enzyme for hydrolysis of triacylglycerol (Newsholme and Crabtree, 1979). This generates the flux both by lipolysis, (in adipose tissue) and by FA oxidation (in muscles).

A flux-generating enzyme has some characteristics:

(i) It catalyses a non-equilibrium reaction in vivo.
(ii) It reaches saturation with its substrate in vivo.

(iii) It is independent of changes in the concentrations of pathway-substrates.

(iv) It responds only to factors external to the pathway.

(v) And most important of all, it generates a flux to which all other enzyme-catalysed reactions in the pathway respond.

Fatty acid mobilization increases during conditions of stress.

Increased sympathetic activity with adrenaline release from the nerve endings stimulates cAMP dependent protein kinase via adenyly cyclase and cAMP. This results in activation of triglyceride lipase leading to hydrolysis of triacylglycerol with consequent increased FA mobilization.

Isotopic techniques reveal that a part of FA formed are again esterified to resynthesize triacylglycerol. This, despite being ATP-consuming reaction, provides a sensitive and delicate control over the mobilization of FA from the adipose tissue.

Catecholamines, glucagon, growth hormone (in presence of glucocorticoids and ACTH) and thyroid stimulating hormone tend to raise the FA level, while insulin and prostaglandins (PG\(_1\) and PG\(_2\)) tend to lower the same.

<table>
<thead>
<tr>
<th>Factors which tend to raise blood FA and FFA</th>
<th>Factors which tend to lower blood FA and FFA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress</td>
<td>Parasympathetic stimulation</td>
</tr>
<tr>
<td>Starvation</td>
<td>Satiety</td>
</tr>
<tr>
<td>Catecholamines</td>
<td>Insulin</td>
</tr>
<tr>
<td>Glucagon</td>
<td>Nicotinic acid</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>Prostaglandins</td>
</tr>
<tr>
<td>Thyroid stimulating hormone</td>
<td>MJ 1999 (by inhibiting adrenaline)</td>
</tr>
<tr>
<td>Diabetics</td>
<td></td>
</tr>
</tbody>
</table>
3. Free fatty acids: These are important vehicle of FA transport from adipose tissue depots to other tissues. The main sources of FFA are triacylglycerol, circulating lipid esters, intestinal chyle and liver. Exogenous triglyceride may account for 10% of FFA during the absorptive phase of fats (Fredrickson et al, 1958).

FFA exists at physiological pH mainly in form of acyl acids, but some anionic dimers may also be present in free solution in equilibrium with FA anions (Spector, 1968). The concentration of FFA in normal humans is about 0.5 mEq./litre (Goodman, 1958; Nutrition Review 1959) and a plasma half-life of 1 - 2 minutes corresponding to a fractional turn-over of 30% - 50% per minute (Fredrickson et al, 1957, 1958; Laurell et al, 1957). All transport of FFA between plasma and cells occurs through the small extracellular unbound FFA pool and this depends upon the concentration-gradients across the cell-membrane (Spector, 1968). This implies that FFA receptors on cell-surface have a very high affinity for FFA in comparision to albumin and the turn-over of the FFA pool takes place at an extraordinarily rapid rate. But Zierler and co-workers (1965) were of the opinion that FFA is most probably transferred directly from binding sites on albumin molecules to acceptor sites on the cell surface, where FFA is an obligatory intermediary. They also demonstrated that outflow of FFA depends on the size of "cellular release FFA pool" and is not influenced by the concentration in the surrounding medium.

Hevel and associates (1963) using Palmitic-1-C\textsuperscript{14} as tracer fatty acid in their experiment of treadmill walking at 3 - 4 miles per hour, obtained average turn-over rate of 27.7 mmol/minute during the second hour in human beings in the post-absorptive state, while the rate was only 7.6 mmol/minute in subjects who were fed carbohydrates in excess of their...
FIG. 9 - LIPID METABOLISM IN MAN

VLDL and chylomicrons are metabolised by lipoprotein lipase. The resulting FFA enters FFA pool 2 for rapid intracellular conversion to triglycerides. This pathway is stimulated by insulin and glucose. Hormone sensitive lipase releases fatty acid into the circulation.
energy needs.

Spitzer and Issekutz (1964), by using arteriovenous differences in FFA level on vessels supplying predominantly muscles (or myocardium), showed FFA removal to the tune of 2 - 4 mEq/minute.

ENDOGENOUS CONTROL OF FFA METABOLISM

I. Control mechanisms - Circulating plasma FFâ level exerts single most important influence on FFA turn-over. Thus all hormonal and other influences that affect the release of fatty acids from adipose tissue (and thereby change arterial FFA level), will also alter the FFA turn-over (Armstrong et al, 1961; Issekutz et al, 1964).

(A). Catecholamines - Increase the mobilization and turnover of FFA.

This may account for the calorogenic effect of catecholamines. This calorogenic response may be composite of several factors, such as redistribution of various substrates (glucose, FFA, pyruvate, Lactate, glycerol, aminoacids), changes in the secretion of other hormones (glucocorticoids, insulin), an increase in the work of heart, increase in protein metabolism and redistribution of blood flow.

Nicotinic acid and "MJ 1999" inhibit catecholamine-induced increase in plasma FFA level (Svedmyr et al, 1967).

(B). Insulin - Insulin administration decreases FFA release (Armstrong et al, 1961). A feedback of plasma FFA on insulin secretion is also present (Greenough et al, 1967; Madison et al, 1968). So acute elevation of plasma FFâ is followed by an increase in plasma insulin level.

II. Fatty acid metabolism in various tissues - FFA serve as the major transport form of lipid that supply oxidizable substrate to the
individual tissues. Because nearly all tissues can utilize fatty acids, the rate of FFA flux is very high, resulting in a complete turnover of the plasma FFA pool in a few minutes under controlled resting conditions. The break-up of FFA turnover is liver 35%, GIT 20%, Skeletal muscle 25%, Myocardium 6%, Kidney 5%, Brain 2%, others 7% (Spitzer et al, 1971).

(A). Myocardium - In the post-absorptive state plasma FFA serve as the major metabolite and may account for 60% - 100% of oxygen consumption by myocardium. Rest 30% - 40% are contributed by lactate and glucose. Presence of ketone bodies suppresses FFA utilization by this tissue.

(B). Skeletal muscle - FFA accounts for 25% - 30% of the energy metabolism in resting muscle. Muscle glycogen and ketone bodies become major metabolites during exercise. Ketone body infusion suppresses the uptake and oxidation of FFA.

(C). GIT - FFA accounts for 20% of energy production. Uptake and oxidation of FFA is proportionate to arterial FFA concentration.

(D). Liver - It utilizes 35% of total FFA flux. This portion does not alter with dietary status or diabetes. The fate of FFA entering the liver may be oxidation to carbon dioxide or ketone bodies or synthesis to TG, phospholipids or cholesterol esters. FFA influx to the liver depends upon plasma FFA levels and the balance between FFA and other substrates which can serve as respiratory fuel.

(E). Kidney - FFA is the most important energy substrate and it directly affects sodium reabsorption. Other important
**Figure 10 - Ketone Body Regulation of FFA Metabolism**

Partial oxidation of FFA to ketone bodies represents an effective disposal of FFA while providing ketogenic fuel for extrahepatic tissues. The result is sparing of glucose as a metabolic fuel.
metabolic substrates are KG, lactate, pyruvate and alpha-ketoglutarate.

(F). **Brain** - Possesses all the enzymes necessary for utilization of glucose, FFA or ketone bodies. Glucose is the major metabolite at rest, while during conditions of "physiological ketosis" (i.e. starvation, exercise, exposure to cold, child birth etc.), ketone bodies and FFA provide major portion of energy.

(G). **Prostaglandins** - PGE$_1$ and PGE$_2$ inhibit lipolysis and decrease the plasma FFA level by interfering with cAMP formation.

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**INHIBITION OF GLUCOSE UTILIZATION BY FATTY ACID OXIDATION**

Fatty acid perfusion (in presence of glucose) inhibits the rate of glucose uptake and glycolysis in isolated rat heart (Garland et al, 1964) and in red skeletal muscles (Rennie and Holloszy, 1977) provided that the preparation is well oxygenated. Thus in heart, diaphragm and red skeletal muscles, fatty acids are not only oxidized in preference to glucose but they also inhibit glucose utilization.

During starvation or severe exercise the blood FA level increases while respiratory quotient decreases from 0.81 to 0.73 indicating a shift from carbohydrate to lipid utilization.

\[
\text{Rate of CO}_2 \text{ output} \quad \frac{R.Q.}{\text{Rate of O}_2 \text{ Uptake}}
\]

\[
\begin{align*}
\text{C}_6\text{H}_{12}\text{O}_6 + 6 \text{O}_2 & \rightarrow 6 \text{CO}_2 + 6 \text{H}_2\text{O} = 6/6 = 1.00 \\
\text{C}_{57}\text{H}_{104}\text{O}_6 + 80 \text{O}_2 & \rightarrow 57 \text{CO}_2 + 57 \text{H}_2\text{O} = 57/80 = 0.71 \\
2\text{C}_3\text{H}_7\text{O}_2\text{N} + 6 \text{O}_2 & \rightarrow (\text{NH}_3)_2\text{CO} + 8 \text{CO}_2 + 5 \text{H}_2\text{O} = 5/6 = 0.83
\end{align*}
\]
This shift occurs without any marked decrease in blood glucose level and implies that lipid-derived fuels are being oxidized in preference to glucose. Hence FA oxidation inhibits glucose utilization or oxidation or both.

Fatty acid oxidation leads to increase in acetyl CoA level, which by inhibiting pyruvate dehydrogenase prevents further conversion of pyruvate into acetyl CoA. This results in excess pyruvate accumulation which goes into gluconeogenic pathway via lactate or alanine.

FA oxidation also increases the mitochondrial citrate concentration, which by inhibiting phosphofructokinase (key glycolytic enzyme) and intermediary reactions inhibits phosphorylation of glucose and thus preserves glucose.

**THE GLUCOSE - FATTY ACID - KETONE BODY CYCLE**

(Stanley, 1981)

When blood glucose (and particularly liver glycogen) concentration decreases, then fatty acids are mobilized from the adipose tissue and these are oxidized by the various tissues. Oxidation of FA specifically inhibits glucose utilization. Previously the reduced rate of mobilization and oxidation of fatty acids was thought to be due to increased blood glucose concentration, but the latest concept attributes this to an increase in the concentration of insulin. Insulin by inhibiting fatty acid mobilization and oxidation increases glucose utilization, this is the homeostatic role of insulin (Newsholme, 1977). This results in blood glucose concentration being maintained near normal level. This further allows delicate control of FA mobilization and oxidation and glucose utilization.

A triglyceride meal followed by injection of heparin or noradrenaline
leads to increased blood FA concentrations, decreased glucose utilization and impaired glucose tolerance. Administration of nicotinic acid (an antilipolytic agent) in human subjects decreases FA concentration and improves glucose tolerance (Stanley, 1981). Likewise inhibitors of FA oxidation (Pent-4- einoic acid), when administered to human subject, produce decrease in blood glucose level. All these are indicative of the in-vivo operation of the control mechanisms.

In the post-absorptive period the brain utilizes 120 gms. glucose daily. This much glucose in completely oxidized to water and carbon dioxide (via pathways of glycolysis, TCA cycle and respiratory chain) and represents a net loss of carbohydrates to the body. As liver glycogen can provide glucose for only 24 hours, any additional glucose must be produced by gluconeogenesis (from muscle protein breakdown) or the brain must use some alternative fuel. In prolonged starvation, the glucose requirement of the brain comes down to only 35 gms. a day while simultaneously rate of KB utilization increases (Owen et al, 1967). The brain possesses all the enzymes necessary for KB utilization and does utilize them pretty well.

The mechanism, whereby KB utilization inhibits glucose utilization in brain is likely to be similar to the one whereby FA oxidation inhibits glucose utilization in muscle. The KB oxidation acts in two ways:

(i) It inhibits pyruvate dehydrogenase activity by increasing concentration of acetyl CoA and the ratio acetyl CoA : CoA, thereby sending pyruvate in the gluconeogenic pathway.

(ii) It inhibits phosphofructokinase and hexokinase, by increasing concentration of citrate with a resultant fall in cerebral glucose utilization.
Fig. 11 - The Glucose-Fatty Acid-Ketone Body Cycle.
The kidney cortex uses about 34 gms. glucose daily in post-absorptive period. But during prolonged starvation, all available glucose is utilized by the anaerobic tissues and brain, while kidney utilizes FA and KB. Similarly, small intestine also oxidizes FA and KB while glucose utilization is decreased. This decreased glucose utilization in small intestine is not due to citrate accumulation, but rather due to a decreased concentration of glycolytic enzymes — hexokinase, phosphofructokinase and pyruvate-kinase (Hansen & Parsons, 1978). Hence ability of KB as alternative fuel for brain, kidney and small intestine helps in conservation of glucose.

ROLE OF KETONE BODIES IN INTEGRATING THE METABOLISM OF MUSCLE, LIVER & BRAIN

Recent studies suggest that KB directly inhibit the rate of protein degradation in muscle and the rate of alanine release in the blood. Thus infusion of alanine into patients recovering from surgery increases the plasma KB concentration and reduces urinary nitrogen excretion. Conversely, infusion of KB in starving man reduces the plasma alanine concentration and the urinary nitrogen excretion.

Possible mechanism of action is that KB increase the concentration of leucine (and other similar branched-chain amino acids) by inhibiting alpha- ketoisocaprate dehydrogenase multienzyme complex. This increased leucine concentration promotes protein synthesis by inhibiting the rate of protein degradation.

Regulation of ketogenesis — The synthesis of acetoacetate and 3-Hydroxybutyrate from fatty acids involves co-operation of the two tissues — adipose tissue (fatty acid mobilization) and liver (synthesis of ketone bodies from fatty acids).
In liver FA are first esterified to fatty acyl CoA, which is again esterified either with glucose-3-phosphate to resynthesize triacylglycerol or with carnitine to form fatty acylcarnitine. Inside mitochondria, fatty acylcarnitine is converted back to fatty acyl CoA; which undergoes beta-oxidation to form acetyl CoA. To ensure ketogenesis, fatty acyl CoA must be directed towards mitochondria; this can involve, either inhibition of triacylglycerol resynthesis, or stimulation of FA transport into mitochondria (by stimulating carnitine-acyl-transferase-I) or a combination of both. Similarly, mitochondrial acetyl CoA can enter (i) TCA cycle (CO₂ production) or (ii) HMG-CoA pathway (KB production); for ketogenesis to occur either inhibition of TCA cycle or stimulation of HMG-CoA pathway or a combination of both is necessary. The capacity of TCA cycle, does, indeed decrease in in-vivo studies; but no change in capacity of HMG-CoA pathway is observed.

Factors which integrate the mobilization of FA (from adipose tissues) and the synthesis of KB from these FA (in liver) are blood levels of insulin, glucagon and KB. Enhanced ketogenesis during starvation is due to decreased level of antilipolytic hormone insulin in presence of increased level of the ketogenic hormone glucagon.

Glucagon inhibits acetyl CoA carboxylase via cAMP and cAMP dependent protein kinase. This results in decreased synthesis of malonyl CoA which de-inhibits carnitine-acyl-transferase-I with resultant increased ketogenesis.

On the other hand high concentrations of KB stimulate secretion of insulin which directly inhibits the rate of FA mobilization from adipose tissue and increases sensitivity of this tissue to the effect of insulin (Green et al, 1979). Ketone bodies thus act as metabolic signals for activation of a sensitive feed-back control mechanism.
Body reacts to any biological insult (injury, anaesthesia or surgery) by series of changes in metabolism and hormone secretion. These changes can, conveniently, be subdivided according to the various phases:

1. Changes caused by injury itself.
2. Modification in changes by anaesthesia.
3. Re-modification of these changes by surgical procedures superimposed on previous injury and anaesthesia.

**METABOLIC CHANGES DURING INJURY** - Cuthbertson (1970) demonstrated the "ebb", "flow" and "necrobiotic" phases after different injuries in man. Sometime a prehypovolemic stage precedes "ebb" phase.

"Ebb" phase may last for 2 days following injury. It is characterized by a diminished capacity for heat production and oxygen consumption is reduced in environment below thermoneutral range (Temperature 28° - 32°C and Relative humidity 30% - 40%). Hyperglycemia seen is directly proportional to degree and nature of injury. Afferent impulses from damaged tissue, volume receptors (hypovolemia) and pressure receptors (hypotension) lead, via reflexes involving mesencephalic and hypothalamic centres, to increased secretion of catecholamines.

During prehypovolemic stage, the carbohydrate (glucose and its polymers glycogen and glucose phosphate) utilization is increased. Depletion of liver and muscle-glycogen soon causes hyperglycemia, up to 4 times of previous level persisting for few hours. Surprisingly the glycogen content of brain remains the same, while that of myocardium actually increases. The glucose disposal rate (R) reduces in proportion to fall in oxygen consumption resulting from impaired thermoregulation following trauma. The concentration of insulin decreases and resistance
to insulin develops which may continue into "flow" phase. The factors implicated for insulin resistance are circulating concentration of adrenaline, pituitary growth hormone and glucocorticoids.

The "flow" phase (i.e. next several days) is characterized by raised basal metabolism, increased heat production and increased oxygen consumption. Type and severity of injury, age, sex, previous nutrition and environmental temperature affect the increase in metabolism. Carbohydrate metabolism shows increased gluconeogenesis and is complicated by the administration of various intravenous infusions. The respiratory quotient shows a shift from carbohydrate to lipid metabolism. The rates of glucose disposal and insulin secretion may reach new peak values.

"Necrobiosis" is the terminal phase in fatal cases. All features of classical untreated shock are seen. Oxygen transport to the cells and tissues progressively deteriorates. Combination of progressive hypoxia and decreased gluconeogenesis leads to a terminal hypoglycaemia. The anaerobic metabolism of glucose leads to pyruvate accumulation both in cells and blood. The lactate/pyruvate ratio also rises.

In a nutshell, mild injury leads to very little metabolic changes, but severe, extensive injuries (multiple fractures, severe burns) are notorious. The extent of changes in such situations may be up to 30% - 40%. The plasma concentration of FFA is sharply increased and disposal rate of plasma chylomicrons or infused fat emulsions is accelerated. Blood glucose concentration is universally raised because increased sympathetic activity nullifies the normal negative feedback control of glucagon.
METABOLIC AND ENDOCRINAL CHANGES DURING SURGICAL PROCEDURES— Surgical procedures evoke an endocrine response (substrates mobilization, a shift towards catabolism, negative nitrogen balance and salt & water retention) in direct proportion to the magnitude of surgical trauma; Thus intra-abdominal procedures evoke a much greater response than the body surface surgery (Clarke, 1970; Clarke et al, 1970) and cardiac surgery with cardiopulmonary bypass induces profound hormonal and biochemical changes (Stanley et al, 1979).

The initial response to surgical trauma is an increased concentration of catabolic hormones (catecholamines, glucagon, cortisol) with concomitantly decreased circulating concentrations of anabolic hormones (insulin & testosterone). Nistrup Madsen and colleagues (1976) demonstrated good correlation between changes in plasma adrenaline and cAMP values. Plasma level of cAMP (a common intracellular second messenger for beta-adrenergic agonists) rises proportionate to the severity of surgery (Nistrup Madsen et al, 1976).

Catecholamines— The more specific and sensitive radioenzymatic assay techniques have resulted in conflicting opinions on the role of circulating catecholamines as mediators of the metabolic response to surgery.

Abdominal surgery increases both adrenaline and noradrenaline values (Halter et al, 1977), while pelvic surgery results in a increase of adrenaline alone (Nistrup Madsen et al, 1976; Engquist et al, 1980). Interestingly, maximum change in plasma adrenaline value was found after reversal of anaesthesia in both types of surgery. Silverberg et al, (1978) and Clutter et al (1980) attributed changes in heart rate, arterial blood pressure, blood glucose, lactate and glycerol levels to increased adrenaline concentration rather than to that of noradrenaline.
Alpha-adrenergic blockade with phentolamine (Allison et al, 1959) and beta-adrenergic blockade with propranolol (Cooper et al, 1980) do not significantly alter the overall metabolic responses. The observation made by Butler et al (1977) that the ideal method of assessing the individual catecholamine response to surgery has yet to be defined, is undoubtedly still valid.

Cortisol and ACTH - Depending upon the severity of surgery, the plasma cortisol level rapidly increases and remains elevated for a variable time after operation (Gordon et al, 1973). The increased cortisol production is secondary to increased ACTH secretion, but the increase in ACTH level is far more than is necessary to produce a maximal adrenocortical response (Thoren, 1974). The normal pituitary-adrenocortical feedback mechanism is no longer effective. ACTH administration during surgery does not increase plasma cortisol any further, while corticosteroid administration fails to abolish the ACTH-cortisol response in postoperative period (Thoren, 1974).

Large doses of ACTH or hydrocortisone in normal subjects resemble many features of surgery (hyperglycemia, protein degradation, sodium and water retention, potassium loss). However this increased cortisol concentration has a "permissive" effect rather than a direct causative role according to present concepts. Thus, severe hyperglycemia of thoraco-abdominal surgery can be markedly decreased in the presence of a normal adrenocortical response (Bromage et al, 1971) and adrenalectomized patients maintained on constant doses of glucocorticoids develop a negative nitrogen balance after operation (Johnstone, 1964).
**Growth Hormone** - Has mixed anabolic and catabolic effects — promotes protein synthesis, is lipolytic and in high concentrations, is diabetogenic (Oyama et al, 1970). Its level increases during surgery (Hall et al, 1978), but does not remain elevated post-operatively even after extensive operations like cardiac surgery (Brandt et al, 1978). In non-stress states growth hormone secretion is stimulated by hypoglycemia, while glucose administration depresses the same. Growth hormone plays a relatively minor role, because a normal metabolic response to surgery is seen in hypophysectomized patients maintained on steroid replacement therapy (Thoren, 1974).

**Glucagon** - Increased plasma glucagon concentrations occur in burns and major injuries (Lindsay et al, 1974) and also in a wide variety of major surgical procedures (Russell et al, 1975). Increased plasma glucagon level up to 4 days, is seen during gastric surgery or surgery with complications. However foster and colleagues (1980) observed normal plasma glucagon level within 48 hours after major abdominal surgery.

Control of glucagon secretion is multifactorial (Alberti et al, 1977). A non-stress induced hyperglycemia produces fall in glucagon level, but this mechanism is not operative in stress-induced hyperglycemia (Unger et al, 1962).

**Insulin** - Plasma insulin level falls during and just after surgery in spite of co-existing hyperglycemia but returns to normal or above-normal values in late post-operative period (Russell et al, 1975).

The relationship between insulin and glucagon secretion is complex. Initially insulin level falls, while glucagon level increases, but later in post-operative period both are increased. Pre-dominance of

Most probably the metabolic response to surgery is the result of the increased activity of all the catabolic hormones in the presence of a reduced activity of the key anabolic hormone — insulin.

PROTEIN METABOLISM — There is an initial decrease in protein synthesis in muscles followed by increased protein catabolism. De-amination of resultant amino acid flux in the liver results in increased urea production and urinary nitrogen excretion. The duration and magnitude of this nitrogen loss is related to severity of surgery and nutritional status of patient (Fleck, 1980). A man of average built may lose upto 0.5 kg. lean tissue mass per day for 4 - 5 days after major abdominal operation, this much loss in severely debilitated patients indicates poor prognosis (Johnstone, 1964).

Alanine derived from muscle protein breakdown, is taken up rapidly during surgery to ensure sufficient hepatic gluconeogenesis (Elia et al, 1980).

CARBOHYDRATE METABOLISM — Hyperglycaemia is proportionate to severity of surgery and values upto 10 mmol/litre may be found during cardiac surgery. This may cause glycosuria (Brandt et al, 1978). Normal neuro-humoral regulation is no longer effective, insulin suppression is seen early in the surgery. Aarima et al, (1974), by using serial intravenous glucose tolerance test, showed decreased glucose utilization and resistance to insulin during surgery. Relative contribution of hepatic glycogenolysis and gluconeogenesis towards hyperglycaemia are controversial (Cooper et al, 1980; Richards, 1980).
FAT METABOLISM - Increased FFA mobilization may account for reduced glucose utilization, but FFA concentration during surgery show little changes (Hall et al, 1978; Kehlet et al, 1979). Heparin administration during surgery causes a large and immediate increase in plasma FFA values due to stimulation of lipoprotein lipase enzyme.

For ketone bodies, values of 250 mmol/litre after cardiac surgery (Brandt et al, 1978) and 2 mmol/litre after hysterectomy (Kehlet et al, 1979) were seen. This wide variation in ketone bodies response to surgery is possibly similar to that seen during starvation (Rich et al, 1979).

ACTIVATION OF RESPONSE - Increase in afferent somatic and autonomic nerve fibre activity is important in initiating the response to surgery (Wilmore et al, 1976), because analgesia per se does not prevent the hormonal changes (Bromage et al, 1971).

The existence of various wound hormones (Prostaglandins, serotonin, acetylcholine and amino acids released by damaged tissue) is somewhat doubtful (Egdahl, 1959), but still may have some role in severe burns and trauma (Wilmore et al, 1976). Haemorrhage, starvation and dehydration all play some role. Premedication and sleep pattern of previous night influence the plasma cortisol values (Oyama, 1973). Infection, prolonged bed rest, hypoxaemia and the biological day-night rhythm also affect this response to surgery.
ENOCRINE AND METABOLIC CHANGES WITH ANAESTHESIA

"The most striking, the most constant and one of the most consequential disturbances of metabolism during anaesthesia is the rise in the glucose and lactic acid content of circulating blood."

(Harris, 1951).

In recent years, this view has not been confirmed in man and in the absence of surgery, anaesthesia with various anaesthetic agents has not been shown to cause a significant increase in the blood sugar level (a parameter most commonly studied by the various workers).

Even deep surgical anaesthesia or profound analgesia can only suppress the afferent impulses (pain etc.) which continue to flow into cerebral cortex along primary pathways and excite cells in appropriate sensory areas.

All anaesthetic agents, as a rule, inhibit and interfere with cellular respiration and enzymatic processes. They affect hepatic as well as myocardial metabolism but cerebral metabolism is relatively unaffected.

Anaesthetic agents affect carbohydrate metabolism (Variable hyperglycaemia, glycosuria, impaired glucose tolerance); Increased concentration of catabolic hormones with decreased concentration of anabolic hormones; Lipid metabolism (lipolysis with little change in plasma FFA, glycerol and ketone bodies levels); protein metabolism (protein sparing effect with variable nitrogen balance and urinary nitrogen-urea excretion).

Spinal anaesthesia without surgery reduces catecholamine levels. Barbiturates interfere with oxidation of Nicotinamide Adenine dinucleotide
dehydrogenase (NADH). Thiopentone-Nitrous oxide anaesthesia with or without relaxants causes little hyperglycemiam. First dose of Propanidid causes no hyperglycemiam, but subsequent doses do so up to variable extent.

**DI - ETHYL ETHER** - This is unique among the inhalational agents in causing a liberation of glucogenic hormones other than catecholamines, as well as raising the blood sugar, in producing lactic acidosis and in failing to lower the elevated FFA level (J.C. Stanley, 1981).

It induces hyperglycemiam (Cullingford, 1966). Oyama and Takezawa (1971) recorded a mean rise of 7 mg/dl in blood glucose over a period of 45 minutes of anaesthesia with ether.

**I - Sympatho-adrenal Response** - Ether increases sympathoadrenal activity producing significant rise in the concentration of circulating adrenaline and noradrenaline (Elliot et al, 1968; Black et al, 1969; Singhal et al, 1982). Studies by Miller and Biscoe (1966) show that ether increases the postganglionic sympathetic discharge.

Black and his colleagues (1969) suggested that this increase in sympathoadrenal activity is an attempt to offset the depressant effects of anaesthetic agent on cardiovascular system.

The hyperglycemia is mainly due to hepatic glycogenolysis (Annamunthodo et al, 1958), is less pronounced in man with liver disease and does not occur in hepatotomized animals. Total sympathetic blockade prevents it (Breuster et al, 1952).

Griffiths (1953) attributed this hyperglycemic response and hepatic glycogenolysis to two factors "the direct action of a hepatotoxin (the anaesthetic agent) on the liver cells" and "sympathetic stimulation acting through sympato-adrenal mechanism". But Cullingford (1966) contended that ether anaesthesia in absence of surgical stimulus seldom produces hyperglycemia. A logical
explanation is that, ether anaesthesia increases level of norepihrenaline alone in man (Price, 1957) in contrast to both adrenaline and noradrenaline in animals (Brewster et al, 1952; Richardson et al, 1957). Since noradrenaline is largely devoid of metabolic effects the difference between animal and human response to ether is obvious.

The sympathetic stimulation caused by ether produces a significant rise in the blood FFA level by increasing the rate of lipolysis (Hanneman et al, 1961; Oyama et al, 1971). Singhal and colleagues (1979) also noted a significant rise in the blood FFA level during ether anaesthesia. But Cooperman (1970) observed no significant rise in blood FFA level with this agent.

II- Adreno-cortical Response - Ether is the strongest stimulant of adrenocortical activity among the various anaesthetic agents (Hammond et al, 1958; Vandam and Moore, 1960). Neither a deep plane of anaesthesia nor a duration of over one hour is necessary to produce significant adreno-cortical response (Oyama et al, 1958). Some workers reported distinct rises in plasma ACTH and cortisol levels following ether anaesthesia. In fact the cortisol response is largely due to surgical stress. The corticosteroids are somehow responsible for insulin resistance seen in patients during stress.

III- Direct response - Ether anaesthesia has a direct effect on carbohydrate metabolism (Bunker, 1962), possibly by interfering with cellular transfer of glucose thereby impeding phosphorylation and subsequent metabolism of glucose. It also inhibits electron transfer at or near the NADH dehydrogenase locus, (Cohen et al, 1972).

Ether causes marked rise in plasma catecholamines and cAMP levels. The catecholamine-induced lipolysis is believed to be
mediated by a cAMP system (Sutherland et al, 1968). Therefore during increased sympathetic nervous activity, plasma FFA levels rise.

Cooperman (1970) in man observed no significant change in FFA level. The marked hyperglycemia seen with ether anaesthesia may cause marked inhibition of FFA release from adipose cells and this may account for no apparent rise in FFA level.

TRI-CHLORO-ETHYLENE - The analgesic concentrations (1%) of this agent cause universal unawareness in the patients (Prior, 1972; Kumar and Saxena, 1977). The acid-base parameters remain remarkably steady and comparable with the control cases (Dobkin and Bayliss, 1962; Kohli, Punnoose, Srihari and Gode, 1977).

I- Sympatho-Adrenal Response - Remarkable cardiovascular stability is seen with low concentrations of this agent in man and animals (Dobkin et al, 1962). Heart rate and arterial blood pressure remain very much stable and no cardiac arrhythmia is seen with such low concentrations (Dobkin et al, 1962; Holmes et al, 1963; Leatherdale, 1966; Kohli, Punnoose, Srihari and Gode, 1977). On the contrary, hypotensive pressures (as low as 80 mm.Hg.) with or without bradycardia due to vagal stimulation, are sometimes seen (Holmes et al, 1963; Prior et al, 1965).

There is no alteration in plasma noradrenaline levels during trichloroethylene anaesthesia (Elliot et al, 1968). Adrenaline is responsible for the cardiac arrhythmias during this anaesthesia in man (Lloyd-Williams et al, 1943; Barnes et al, 1944; Richards et al, 1962) but all such arrhythmias dissipated when the inhaled concentration of trichloroethylene is reduced and the hypercarbia is corrected (Malhotra et al, 1977).
It causes hyperglycemia and lactic acidosis. The mechanism of this hyperglycemia is not well understood (Sikh, 1966). The possible explanations are that this agent enhances breakdown of tissue glycogen and a diminished peripheral glucose utilization due to depressed metabolism (Krantz and Carr, 1965) and by increasing the level of circulating catecholamines (Dobkin et al, 1962; Dixit, 1972; Lakshmi et al, 1973; Dev et al, 1977; Singh et al, 1977). It stimulates the sympathetic receptors and this causes increased level of circulating catecholamines, which results in activation of adenyl cyclase- cAMP- lipoprotein lipase system with resultant increased lipolysis from the adipose tissue and increased level of blood FFA.

II- Direct Response - Olson and Spencer (1968) observed an increase in the mitochondrial volume change caused by ATP or ADP, an increase in ATP hydrolysis and an increase in mitochondrial respiration.

HALOTHANE:--


A combination of central autonomic paresis, ganglionic blockade and supression of peripheral action of the sympathetic
transmitter tends to prevent the rise of plasma noradrenaline during halothane anaesthesia (Price et al, 1963; Price et al, 1966; Miller and Biscoe, 1966). Suppression of baroreceptors allows halothane to exert its direct depressant effects on heart and peripheral vasculature, without the usual compensatory mechanism being brought into play (Price et al, 1963).

Reisener and Lippmann (1975) observed cardiac dysrhythmia with subcutaneous infiltration of adrenaline (1:100000 — 1:300000) during halothane anaesthesia, but Gilani et al (1982) found no untoward cardiovascular effect. This also suggests peripheral sympathetic blockade during halothane anaesthesia.


II- Direct Response - Halothane has been known to inhibit the glycolytic enzymes (Schweizer et al, 1969) and the cellular uptake of glucose (Green, 1965; Ngei, 1972). Halothane also blocks electron transfer between NADH & flavoproteins and depresses oxygen uptake by the cells. It is an uncoupler of oxidative phosphorylation (Miller and Hunter, 1970, 1971). It also depresses FFA uptake by the myocardium.
(Merin et al., 1971).

Makelainen (1974) attributed the rise in plasma FFA following halothane anaesthesia to stimulation of beta-adrenergic receptors leading to an increased lipolysis via the adenyl cyclase-cAMP-lipase system. Halothane also depresses FFA uptake by myocardium. Fatty acid administration leads to a decrease in the halothane inhibition of oxygen consumption, gluconeogenesis and urea synthesis.

Thus it can be seen that the influence of modern inhalation and intravenous agents, on hormone secretion and metabolism is small as compared to that of surgical stimulation provided that hypoxaemia, acidosis and hypothermia are avoided (Traynor et al., 1981). Indeed halothane may even be beneficial as it has been shown to reduce adrenaline secretion in-vitro and in-vivo (Roizen et al., 1974; Halter et al., 1977).

The neuro-endocrine response to trauma appears to have evolved to assist survival in a more primitive environment by providing appropriate substrates to maintain vital functions. However in modern anaesthetic and surgical practice, where severe physiological disturbances are prevented or rapidly treated with prompt administration of suitable substrates, any benefits of this response are no longer apparent. The aim for the future must be the safe prevention of surgically induced, adverse hormonal and metabolic changes to ensure well-being of the patients (Traynor and Wall, 1981).